

EXHIBIT A

Exhibit 3

**IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA
CLARKSBURG DIVISION**

REGENERON PHARMACEUTICALS, INC.,

Plaintiff,

v.

MYLAN PHARMACEUTICALS INC.,

Defendant.

Case No. 1:22-cv-00061-TSK

JURY TRIAL DEMANDED

**OPENING EXPERT REPORT OF KARL G. CSAKY, M.D., Ph.D. REGARDING
INFRINGEMENT OF U.S. PATENT NOS. 11,253,572 AND 10,888,601**

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I. INTRODUCTION

1. My name is Karl Csaky, and I am a medical doctor specializing in vitreoretinal diseases. A copy of my CV is attached as Exhibit A and incorporated here by reference.
2. I have been retained by Plaintiff Regeneron Pharmaceuticals, Inc. (“Plaintiff” or “Regeneron”), as an independent expert witness in the above-captioned case. This expert report sets forth my analyses and opinions based on my knowledge, experience, and the materials I have considered, which are cited herein and set forth in Exhibit B.
3. I understand Defendant Mylan Pharmaceuticals Inc. (“Mylan” or “Defendant”) seeks FDA approval of Biologics License Application (“BLA”) No. 761274 to manufacture and sell a biosimilar version of Regeneron’s EYLEA® product (the “Biosimilar Product”) called YESAFILI™, which is sometimes referred to in Mylan’s documents as M710 or MYL-1701P. In this report, I have been asked to provide my expert opinion regarding whether Mylan would induce infringement of two of Regeneron’s patents if Mylan markets YESAFILI™ upon approval by the FDA.
4. In particular, I have been asked to consider whether, by marketing YESAFILI™, Mylan will induce infringement of claims 1–23 and 25–28 of U.S. Patent No. 11,253,572 (“the ’572 patent”), and claims 5–9, 11–12, 15–17, 19, 21, 23–25, 27–28, and 31–33 of U.S. Patent No. 10,888,601 (“the ’601 patent”). The inventor of both the ’572 and ’601 Patents is Regeneron scientist Dr. George Yancopoulos, and throughout this report I refer to the ’572 and ’601 Patents collectively as the “Yancopoulos Patents.”
5. If asked, I will be prepared to present a basic tutorial to explain the terms and concepts related to the opinions set forth in my expert report, as well as to provide further background on angiogenic eye disorders, their methods of treatment, the state of the art, the level

of skill in the art, and the patents at issue. That tutorial may include demonstrative exhibits and models.

II. SUMMARY OF OPINIONS

6. Below, I provide a detailed explanation of my opinions concerning infringement, as well as relevant background material regarding the subject matter of the Yancopoulos Patents, including angiogenic eye disorders, their treatment, and Eylea® (aflibercept). The following paragraphs summarize some of my opinions in this matter at a high level. This summary is not meant to limit the opinions expressed below in greater detail, but instead to provide a general overview of the subject matter of my testimony.

7. In my opinion, if Mylan markets YESAFILI™ in accordance with its proposed labeling, Mylan will induce infringement of each of claims 1–23 and 25–28 of the '572 patent. If Mylan markets YESAFILI™ in accordance with its proposed labeling, physicians will in fact perform the methods claimed in each of claims 1–23 and 25–28 of the '572 patent, and thereby commit acts of direct infringement. By virtue of YESAFILI™'s proposed labeling and other conduct, Mylan will recommend, encourage, and promote this result.

8. In my opinion, if Mylan markets YESAFILI™ in accordance with its proposed labeling, Mylan will induce infringement of each of claims 5–9, 11–12, 15–17, 19, 21, 23–25, 27–28, and 31–33 of the '601 patent. If Mylan markets YESAFILI™ in accordance with its proposed labeling, physicians will in fact perform the methods claimed in each of claims 5–9, 11–12, 15–17, 19, 21, 23–25, 27–28, and 31–33 of the '601 patent, and thereby commit acts of direct infringement. By virtue of YESAFILI™'s proposed labeling and other conduct, Mylan will recommend, encourage, and promote this result.

III. QUALIFICATIONS

9. I received my Bachelor of Arts from Vanderbilt University in 1978. In 1983, I received my Ph.D. from the University of Louisville's Department of Pharmacology as well as my M.D. from the University of Louisville's School of Medicine. From 1983-1985, I completed an internship in medicine at Duke University. After graduating, I became a Fulbright Scholar at the University of Essen Eye Clinic in Essen, West Germany, where I remained from 1985–1986.

10. After my Fulbright, I was a research training fellow from 1986 to 1987 at Estelle Doheny Eye Foundation, which is affiliated with the University of Southern California. I then trained as a resident in ophthalmology at Washington University from 1987-1990. From 1990-1991, I completed a fellowship in Medical Retina at the Wilmer Eye Institute, Johns Hopkins University before becoming a Biotechnology Fellow in molecular biology at the National Cancer Institution in Bethesda, Maryland from 1991-1993. In the laboratory we worked on the use of various immunoadhesins (similar in biology to aflibercept) and their use in studying various aspects of cancer biology including neovascularization.

11. My first roles post-fellowships were at the National Eye Institute, National Institutes of Health. From 1993-1998, I was the Medical Officer there and from 1998-2004, I was the Tenure-Track Investigator, and then in 2004, I was promoted to Tenured Senior Investigator. During my time at the National Eye Institute I was involved in both clinical research and patient care in the retina clinic as well as running a laboratory on the study and treatment of various retinal diseases. I also worked closely with the Food and Drug Administration and chaired the first NEI/FDA Ophthalmic Clinical Trial Design and Endpoints Symposium.

12. From 2007–2009 I was a tenured Associate Professor in the Department of Ophthalmology, Duke University Medical School. In this job I had extensive clinical responsibilities in various outpatient clinics.

13. Beginning in 2009, I joined, part-time as a partner, the Texas Associates, one of the largest private practice retina practices in the US. My job included managing patients with retinal diseases including overseeing all of their clinical trials.

14. At the same time, I joined Retina Foundation of the Southwest and moved from Senior Scientist to Managing Director to Medical Director. In 2020, I began my current role as Chief Executive and Chief Medical Officer at the Retina Foundation of the Southwest.

15. I have more than 30 years of experience in ophthalmology treating retinal diseases and conducting both basic and clinical research regarding retinal diseases.

16. I am an author of more than 140 peer-reviewed scientific publications and book chapters, most of which pertain to ophthalmology, including articles discussing inhibition of VEGF for treating neovascular AMD, comparison of AMD treatment trials, eye drop treatments versus injection treatments for neovascular AMD, lens extraction in patients with diabetic retinopathy, aflibercept and diabetic macular edema in a clinical trial, and more. I have also written extensively regarding angiogenic eye disorders generally, including DME, RVO, and/or DR.

17. I am an invited speaker both nationally and internationally and lecture to colleagues, fellows and ophthalmology residents on the various subjects pertaining to the diagnosis and treatment of retinal diseases including the use of anti-VEGF agents. I am also a member of several professional societies relating to my work on retinal diseases, including the Macula Society, Retina Society, and American Academy of Ophthalmology, ARVO (the

Association for Research in Vision and Ophthalmology), the American Ophthalmological Society and the American Society of Retinal Specialists (“ASRS”), and was a member of the Executive Committee of the Macular Society from 2012 to 2015. In 2014, I was chair of the ASRS AMD Genetics Task Force. I regularly attend and give lectures at various conferences and other events held by these and other professional societies to exchange knowledge with other clinicians and remain well informed about developments and treatment options in my field.

18. I have substantial experience designing and participating as an investigator in clinical trials for retinal diseases. For example, I have been involved in multiple trials both as an investigator and as a member of various Data and Safety Monitoring Committees.

19. Since I began practicing in 1991, I have treated patients with the retinal diseases relevant to this case—namely neovascular (*i.e.*, “wet”) age-related macular degeneration (“AMD”), diabetic macular edema (“DME”), diabetic retinopathy (“DR”), and retinal vein occlusion (“RVO”), including both branched RVO (“BRVO”) and central RVO (“CRVO”). Collectively, these diseases are often referred to as “angiogenic eye disorders.” I estimate I have seen on average 50 – 100 patients/week with these angiogenic eye disorders, and, now that such anti-VEGF drugs are available, I have often treated such patients using intravitreal injections. I estimate I have performed dozens of intravitreal injections every week.

20. Additional details of my academic background, technical experience and list of publications are set forth in my curriculum vitae, attached as Exhibit A.

21. I am being compensated for my work in this case at my ordinary consulting rate of \$950.00 per hour. My compensation is in no way tied to the outcome of this case or to the opinions I express.

22. I have not testified at trial or by deposition in the last 5 years.

23. My opinions and views set forth in this report are based on my clinical experience, education, training, and research, as well as the materials cited herein and listed in Appendix B.

IV. BACKGROUND

24. This section is intended to provide relevant background about angiogenic eye disorders, treatment options for angiogenic eye disorders, and the manner in which Eylea® is used to treat such diseases.

A. Angiogenic Eye Disorders

25. Angiogenic eye disorders involve the unwanted growth of abnormal blood vessels in the retina, and/or leakage from damaged blood vessels in the retina. Without treatment, these disorders can cause catastrophic vision damage, even blindness and thereby dramatically impact patient quality of life.¹ Examples of angiogenic eye disorders include retinal vein occlusion (“RVO”), diabetic retinopathy (“DR”), diabetic macular edema (“DME”), and “wet” or “neovascular” age-related macular degeneration (“AMD”).² One characteristic shared by each of these angiogenic diseases is the presence of high levels of a protein called vascular endothelial growth factor (“VEGF”) in the eye.³ VEGF’s normal role is to trigger formation of new blood vessels supporting the growth of the human body’s tissues and organs. But when cells secrete

¹ Young Gun Park et al., *New Approach of Anti-VEFG Agents for Age-Related Macular Degeneration*, Journal of Ophthalmology, 2012, at 1 (“Park”); Jeffrey S. Heier, *VEGF Trap-Eye for Exudative AMD*, Retinal Physician, April 1, 2009, at 1, available at <https://www.retinalphysician.com/issues/2009/april-2009/vegf-trap-eye-for-exudative-amd> (“Heier”).

² Anthony P. Adamis, *Ocular Angiogenesis: Vascular Endothelial Growth Factor and Other Factors*, in *Retinal Pharmacotherapy* 23, 23 (Quan Dong Nguyen et al. eds., 2010) (“Adamis”).

³ Adamis at 23.

too much VEGF into the eye, abnormal blood vessels can grow in the eye underneath the macula and retina. These abnormal blood vessels can leak blood or other fluids, blurring central vision and potentially causing blindness.⁴ VEGF can also cause an increase in the vascular permeability of retinal vessels leading to such conditions as diabetic macular edema and macular edema associated with retinal vein occlusions. Before the emergence of anti-VEGF agents (described below), patients with these angiogenic disorders were typically treated using laser ablation and/or photodynamic therapy—options that often did not improve vision significantly and also carried the risk of negative outcomes, such as reduced vision caused by retinal scarring.⁵ I provide more details regarding AMD, DME, RVO, and DR below.

1. AMD

26. Wet AMD affects a patient's central vision and can often be severe—it is the most common cause of severe vision loss among those 50 years old and older.⁶ Aside from age, other risk factors for wet AMD include smoking, high blood pressure, and a diet high in saturated fat.

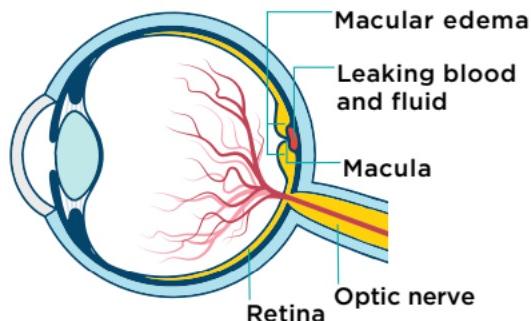
27. The retina is the light-sensitive tissue that lines the inside of the eye. The macula is a small, important area in the center of the retina that is needed to see what is directly in front of you. Wet AMD is caused when abnormal blood vessels grow beneath the retina and leak

⁴ Adamis at 23.

⁵ Pierluigi Iacano et al., *Antivascular Endothelial Growth Factor in Diabetic Retinopathy*, 46 Devs. in Ophthalmology 39, 39 (2010) ("Iacono").

⁶ Philip J. Rosenfeld et al., *Age-Related Macular Degeneration*, in Ophthalmology 658, 658 (Myron Yanoff eds., 2009) ("Rosenfeld").

blood and other fluid, leading to a large blind spot in the center of a patient's vision.⁷ The cartoon below depicts an eye suffering from wet AMD.⁸



28. Patients with advanced AMD often lose the ability to see faces, read small print, and drive. Symptoms include vision blurriness, black spots, and wavy lines, which can get worse over time.⁹ AMD can also lead to blindness.¹⁰

⁷ David S. Boyer et al., *A Phase IIIb Study to Evaluate the Safety of Ranibizumab in Subjects with Neovascular Age-related Macular Degeneration*, 116 Ophthalmology 1731, 1731 (Sept. 2009) (“Boyer”); Niaz Islam, *Ophthalmology: Diseases and disorders*, in *Ophthalmology Dermatology ENT* 66, 66 (Dan Horton-Szar eds., 2009) (“Islam”).

⁸ *Wet AMD*, Eylea® (aflibercept) Injection Wet AMD Patient Pamphlet at 3, available at https://eylea.us/resource/1661445553000/Eylea_Assets_pdfWetAMD/wet-amd-patient-pamphlet.pdf (“Wet AMD Patient Brochure”).

⁹ *Wet AMD*, Eylea® (aflibercept) Injection Wet AMD Patient Pamphlet at 3, available at https://eylea.us/resource/1661445553000/Eylea_Assets_pdfWetAMD/wet-amd-patient-pamphlet.pdf (“Wet AMD Patient Brochure”).

¹⁰ Islam, *supra* note 7, at 66; *About Eye Conditions That Affect the Retina*, Eylea® (aflibercept) Injection, available at <https://eylea.us/s/about-eye-conditions#symptom-slider>.

Wet AMD symptoms may include:



Blurriness in the center of your vision



Straight lines that look wavy



Colors that look dull and washed out



Blind spots or patches



Objects that seem farther away than they really are

If you're experiencing symptoms, it's important to talk to your retina specialist about it.

29. Before the emergence of anti-VEGF agents, wet AMD patients had a poor prognosis among those diagnosed with ocular angiogenic disorders, given the rapid vision loss that could occur and the fact that available treatment options could do no more than reduce the speed of vision loss or reduce the amount/area of vision loss.¹¹ Among patients with angiogenic eye disorders, AMD patients are particularly susceptible to delays in treatment—waiting too long to get treatment or receiving insufficient/unacceptably infrequent treatment can lead to irreversible vision loss more quickly than in other angiogenic disorders.¹²

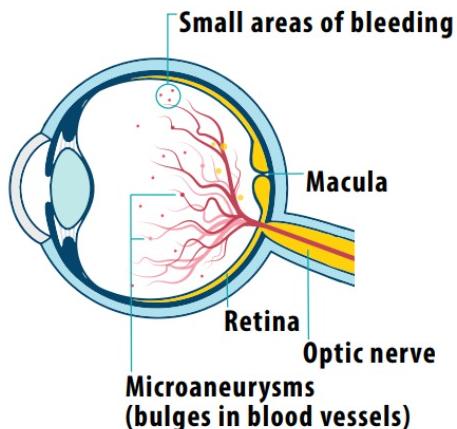
2. DR

30. DR occurs when too much blood sugar damages blood vessels in the retina. DR is the leading cause of new blindness in people ages 20 to 74 years old in the United States, and

¹¹ Park, *supra* note 1, at 1, 5.

¹² Rosenfeld, *supra* note 6, at 658 (“[W]et AMD is responsible for the majority of the severe vision loss and it usually occurs over weeks to months.”); Susan Watkinson, *Issues in Ophthalmic Practice: Current and Future Challenges* 189 (2009) (“Watkinson”).

is the most common diabetic eye disease.¹³ An image showing an eye suffering from DR is depicted below.¹⁴



31. As a result of DR, the retina—which is in the back of the eye—may not receive enough oxygen or nutrients. Blood vessels in the eye can become swollen and can leak blood into the retina. Early DR may not produce symptoms, but moderate DR can cause blurred vision of floating spots. If DR progresses, it can reach its most advanced stage, which is called proliferative DR. In proliferative DR, increased growth of fragile, new blood vessels occurs, leading to swelling and blood vessel leakage.¹⁵

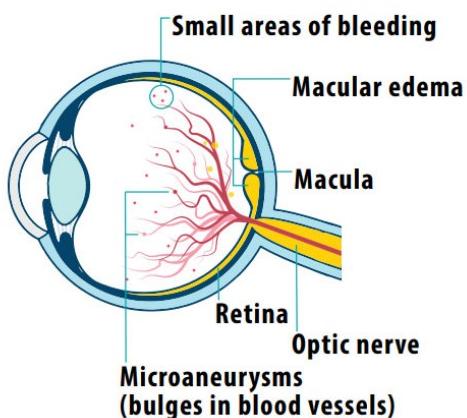
¹³Diabetic Retinopathy (DR), Eylea® (aflibercept) Injection DR Patient Pamphlet at 2, available at https://eylea.us/resource/166144552000/Eylea_Assets_pdfDR/dr-patient-pamphlet.pdf (“DR Patient Pamphlet”).

¹⁴ Diabetic Retinopathy (DR), Eylea® (aflibercept) Injection DR Patient Pamphlet at 2, available at https://eylea.us/resource/166144552000/Eylea_Assets_pdfDR/dr-patient-pamphlet.pdf (“DR Patient Pamphlet”).

¹⁵ About Eye Conditions That Affect the Retina, Eylea®(aflibercept) Injection, available at <https://eylea.us/s/about-eye-conditions#symptom-slider>.

3. DME

32. DME is a complication of DR, and so also occurs when too much blood sugar damages blood vessels in the retina.¹⁶ This can cause blood vessels to leak blood into the retina, leading to swelling of the macula, and can also deprive the retina of oxygen and nutrients.¹⁷ The image below depicts an eye suffering from DME.¹⁸



¹⁶Thomas A. Ciulla, M.D., *Diabetic Retinopathy and Diabetic Macular Edema: Pathophysiology, screening, and novel therapies*, in Diabetes Care 2653 (2003) (“Ciulla”) (describing generally relationship between DME and DR).

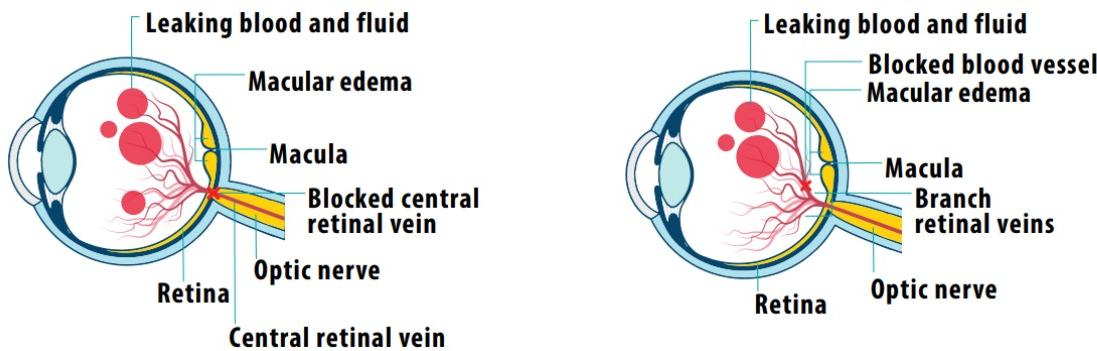
¹⁷ Thomas A. Ciulla, M.D., *Diabetic Retinopathy and Diabetic Macular Edema: Pathophysiology, screening, and novel therapies*, in Diabetes Care 2653 (2003) (“Ciulla”) (describing generally relationship between DME and DR).

¹⁸ *Diabetic Macular Edema (DME)* slide 2, in DME Patient Pamphlet, available at https://eylea.us//resource/1661445551000/Eylea_Assets_pdfDME/dme-patient-pamphlet.pdf, (“DME Patient Pamphlet”); Regeneron provides interactive methods of understanding DME symptoms on its website, as well as an application available for download onto mobile phones, called “In My Eyes”. *About Eye Conditions That Affect the Retina*, Eylea® (aflibercept) Injection, available at <https://eylea.us/s/about-eye-conditions#symptom-slider>; In My Eyes Application (described at <https://eylea.us/s/vr-experience>).

33. DME can cause blurriness in a patient's center vision, straight lines to look wavy, dull or washed out colors, and blind spots or blind patches.¹⁹ DME symptoms can worsen over time.²⁰

4. RVO

34. RVO occurs when a blood vessel in the retina becomes blocked, for instance by a blood clot. The blockage can cause leakage into the macula, leading to vision loss or blurring. Macular edema following central RVO occurs when the central retinal vein is blocked. Macular edema following branch retinal vein occlusion occurs when a vein that branches out from the central retinal vein is blocked. Both of these conditions cause fluid to leak into the macula. Below, the image on the left depicts an eye suffering from macular edema following central RVO, while the image on the right depicts an eye suffering from macular edema following branched RVO.²¹



¹⁹Javier Montero, *Diabetic Retinopathy I* 138, in *Retina and Vitreous* (Jose Maria Ruiz Moreno eds. 2009) (“Montero”).

²⁰Ciulla at 1.

²¹ *Macular Edema Following Retinal Vein Occlusion (MEfRVO)* slide 2, in *RVO Patient Pamphlet*, available at https://eylea.us/resource/1661445553000/Eylea_Assets_pdfRVO/rvo-patient-pamphlet.pdf (“MEfRVO Patient Pamphlet”).

35. Macular edema following RVO can cause a number of visual symptoms, including blurriness in the center of vision, blind spots or patches, straight lines that look wavy, and general vision loss.²²

B. Treatment of Angiogenic Eye Disorders Before Eylea®

36. By the 1990s, scientists began to develop medications that were designed to inhibit VEGF to treat angiogenic eye disorders, to improve patient outcomes, including preventing further loss of vision or even improving vision.²³

37. The first anti-VEGF agent approved for treatment of an angiogenic eye disorder was Macugen® by Eyetech/Pfizer, which was approved to treat AMD in 2004 when administered via intravitreal injection once every six weeks.²⁴ Macugen® was approved after two phase 3 studies—the primary efficacy measurement in these studies was whether or not patients²⁵ lost fewer than 15 letters of visual acuity.²⁶ These studies showed that patients on Macugen® continued to lose vision, but did so more slowly than those who received sham

²² *About Eye Conditions That Affect the Retina*, Eylea® (aflibercept) Injection, available at <https://eylea.us/s/about-eye-conditions#symptom-slider>; In My Eyes Application (described at <https://eylea.us/s/vr-experience>).

²³ Macugen Label (2004) at 2; Lucentis Label (2006) at 5.

²⁴ Letter from Jonca C. Bull, Dir., Office of Drug Evaluation V, CDER, to Loni da Silva, Vice President, Glob. Regulatory Affairs, Eyetech Pharm., Inc. (Dec. 17, 2004); Macugen Label (2004) at 3-5, 7.

²⁵ The POSA reading the claims would understand “patients” to include treatment of patients in clinical practice, which is an ordinary usage of that word. In my opinion, the POSA would not understand “patients” to mean exclusively clinical trial subjects, even if such subjects are also sometimes referred to as “patients.”

²⁶ Macugen Label (2004) at 4.

treatment.²⁷ “Sham” treatment refers to inactive treatment that is designed to closely resemble the active treatment in a clinical study.

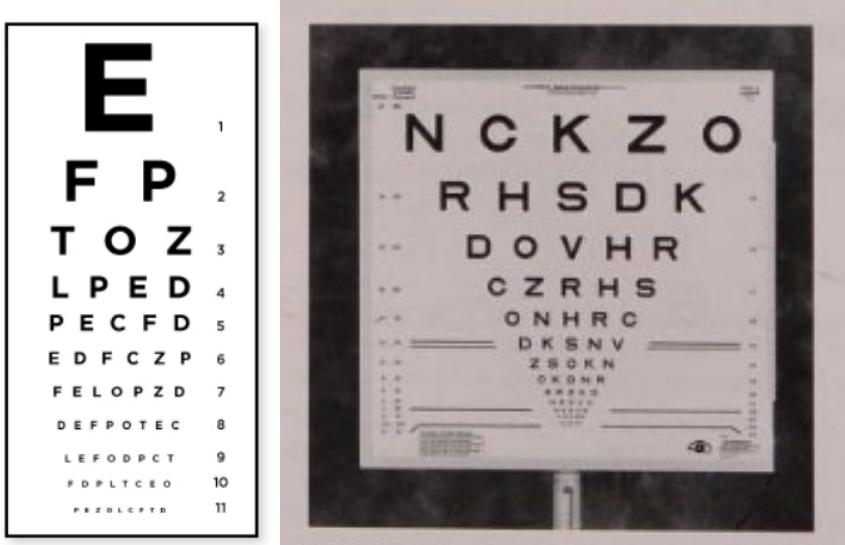
38. Visual acuity is a measurement of a patient’s vision, frequently assessed and quantified according to how many lines or letters a patient can read from an eye chart. There are two primary eye charts used in the measurement of visual acuity—the Snellen chart and the ETDRS chart. Both charts are used in clinical practice and in research.²⁸ A Snellen chart is depicted below on the left,²⁹ and an ETDRS chart on the right.³⁰

²⁷Macugen Label (2004) at 4.

²⁸See Nachankar Tr. 201:7–15 (“Q....So ETDRS and Snellen charts are both ways to assess BCVA of a patient in a doctor’s office?...A. Yeah, yes, from my perspective”), Nachankar Tr. at 201:21 - 202:4 (“Q. So Both ETDRS and Snellen charts are also ways to assess BCVA of a subject in a clinical trial, correct?...A. In our study, we used the ETDRS chart for BCVA assessment...”); see David Miller, *Visual Acuity Testing* 56, in Ophthalmology Third Edition, (Myron Yanoff Ed. 2009) (“Miller”) (describing how Snellen is traditionally measured for patients); see E.M. Kohner, *Photocoagulation for proliferative diabetic retinopathy: a randomised controlled clinical trial using the xenon -arc* 109, in Diabetologia (1984) (“Kohner”) (using Snellen chart to measure visual acuity in clinical trial); see Avila at 2 (use of ETDRS chart in clinical trial). I have used ETDRS charting in my own clinical practice.

²⁹ VISUAL ACUITY IN YOUNG CHILDREN – WHAT IS “NORMAL”? , ForLittleEyes.com, available at, <https://forlittleeyes.com/2009/07/25/visual-acuity-in-young-children-what-is-normal>; see Marcos P. Avila, *Twelve-Month short-term safety and visual acuity results from a multicenter prospective study of epiretinal strontium-90 brachytherapy with bevacizumab for the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration* 4, in British Journal of Ophthalmology, (November 19, 2008) (“Avila”) (referencing ETDRS Snellen equivalent of 20/40 to 20/320 for patient eligibility criteria in 12 month study of treatment of subfoveal CNV).

³⁰ *Visual Acuity*, in Clinical Optics at 110 (2009), available at <https://archive.org/details/clinicaloptics0000unse/page/110/mode/2up?q=contrast+sensitivity&view=theater> (“Clinical Optics”).



Visual acuity values measured using a Snellen chart can be easily equated to ETDRS scores, and vice-versa, and that is routinely done.³¹

39. After Macugen® was approved, physicians began reporting off-label use of Genentech's cancer medication, the anti-VEGF agent Avastin® (active ingredient bevacizumab).³² However, the next anti-VEGF agent to be approved for ocular disease was

³¹ MYL-AFL0089404 at -0089407 (noting patients in Mylan's Phase III study comparing YESAFILI to Eylea involved admitted patients with "best corrected visual acuity of 73 to 38 ETDRS letters, or Snellen equivalent of 20/40 to 20/200"); see Ganapathi Tr. 92:18–92:21 ("Q. What are the other methods that can be used to measure best corrected visual acuity? A. Instead of ETDRS chart, you can use Snellen chart."), Ganapathi Tr. at 96:11–16 ("Q. What is a Snellen equivalent? A. There is a conversion chart where ETDRS letter range is compared with or could be equivalence to Snellen's scope. This is an equivalence to Snellen scope because Snellen's is more popular many times in practice."); Moke, *A computerized method of visual acuity testing: Adaptation of the early treatment of diabetic retinopathy study testing protocol*, Am J. Ophthalmology 194-205 (2003) ("Moke") at 198 (Table 2); see also *infra*, at Section VI.3.4.b.1.

³² Michels S., et al., *Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration: twelve-week results of an uncontrolled open-label clinical study*, Ophthalmology, 112:1035–1047 (2005) ("Michels 2005"); Rosenfeld P.J. et al., *Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin) for neovascular age-related macular degeneration*, Ophthalmic Surg Lasers Imaging. 36:331–335 (2005); Salvatore Grisanti, M.D., *Bevacizumab: Off-label use in ophthalmology* 418, in Indian Journal of Ophthalmology Vol. 55 No. 6, (2007), available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2635984/>, ("Grisanti").

Genentech's Lucentis® (active ingredient ranibizumab).³³ Genentech conducted two phase 3 clinical trials (called MARINA and ANCHOR) in patients with wet AMD. In MARINA, patients received 24 monthly injections of 0.5 mg Lucentis, or 24 monthly sham injections.³⁴ Again, the primary efficacy measure was patients who lost fewer than 15 letters after 12 months.³⁵ In MARINA, one year results showed that almost 95% of patients receiving Lucentis® either maintained their vision or experienced vision gain after 12 months,³⁶ and average vision gains were maintained through month 24.³⁷ On average, patients who received sham injections lost 10.5 letters of vision, while subjects who received 0.3 mg of Lucentis® gained 6.5 letters of vision and subjects who received 0.5 mg of Lucentis® gained 7.2 letters of vision.³⁸

40. In ANCHOR, patients received either monthly injections of Lucentis® (0.3 mg or 0.5 mg) plus sham photodynamic verteporfin therapy or else received monthly sham injections along with (real) photodynamic verteporfin therapy.³⁹ Mean gains in visual acuity for patients receiving Lucentis® ranged from 8.1 to 10.7 letters, while patients who received sham injections lost on average 9.8 letters of visual acuity.⁴⁰

³³ Lucentis Approval Letter (2006).

³⁴ Rosenfeld (2006) at 2-3.

³⁵ Lucentis Label (2006) at 6.

³⁶ Genentech 2006 Press Release at 1.

³⁷ Rosenfeld (2006) at 11.

³⁸ Genentech 2006 Press Release at 4.

³⁹ Brown (2009) at 1.

⁴⁰ Brown (2009) at 1-4.

41. Lucentis® was approved for the treatment of wet AMD in June 2006.⁴¹ The approved treatment regimen was monthly injections of 0.05 mL.⁴² Lucentis was later approved for treatment of other angiogenic eye disorders—for example, macular edema following retinal vein occlusion, diabetic macular edema, diabetic retinopathy in patients with DME, myopic choroidal neovascularization, and diabetic retinopathy (2017).⁴³

42. Macugen® and Lucentis®—along with Avastin®, when it is used off-label in ocular indications—are each administered by intravitreal injection, which is an injection into the eye. In particular, the needle is placed into the vitreous of the eye, which is the jelly-like substance that fills the middle of an eyeball between the lens and the retina. An image of an intravitreal injection from a 2014 article is shown below, and these images equally reflect the procedure as of 2010.⁴⁴

⁴¹ Lucentis Approval Letter (2006); Lucentis Label (2006).

⁴² Lucentis Label (2006).

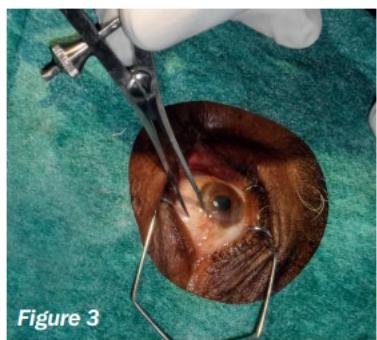
⁴³ Lucentis Label (2018).

⁴⁴David Yorston, *Intravitreal injection technique*, in Community Eye Health Journal Vol. 27 Issue 87, (2014) available at <https://www.cehjournal.org/wp-content/uploads/Intravitreal-injection-technique.pdf>.



Abba Hydara

Abba Hydara



Abba Hydara

Abba Hydara

43. The image below shows the interior of the eye—the vitreous—into which the drugs are injected.⁴⁵

INTRAVITREAL INJECTION



⁴⁵ *Intravitreal Injection*, in Vitreous Retina Macula Consultants of New York, available at <https://www.vrmny.com/procedures/intravitreal-injection/>.

44. As the above images suggest, intravitreal injections have drawbacks. They are a burdensome method of administering medication, because patients must travel to the office of an ophthalmologist—typically a retinal specialist—who administers such injections. Patients with angiogenic eye disorders are often elderly, and sometimes must travel great distances to reach appropriate care—often with a relative or caregiver assisting. Intravitreal injections also require careful procedure to avoid risk of side effects—most notably infection—and thus are burdensome on physicians as well, in addition to being a costly procedure using costly medication.⁴⁶ Intravitreal injections also carry the risks of endophthalmitis, inflammation, and retinal detachment.⁴⁷ The injection process is itself unpleasant for most patients, including due to the anxiety resulting from having such an injection in one's eye. As a result, the retinal community was in search of a treatment regimen that reduced the frequency of injections required to effectively treat patients.⁴⁸

45. Unfortunately, most efforts to develop such a regimen failed. Genentech conducted several studies investigating less frequent dosing of Lucentis®, but each of these studies, including SUSTAIN, EXCITE, PrONTO, SAILOR, and PIER, showed that less frequent dosing of Lucentis® produced inferior results when compared with monthly dosing of Lucentis®. Indeed, the 2006 label for Lucentis stated that “[a]lthough less effective, treatment may be reduced to one injection every three months after the first four injections if monthly

⁴⁶ Alisa M. Shea, MPH, *Resource Use and Costs Associated with Diabetic Macular Edema in Elderly Persons*, in Arch. Ophthalmology Vol. 126 No. 12 1748 (2008) (“Shea”).

⁴⁷ Heier (2012) at 1.

⁴⁸ Heier (2012) at 1 (“describing extensive efforts to decrease injection and monitoring frequency”).

injections are not feasible. Compared to continued monthly dosing, dosing every 3 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following 9 months. Patients should be evaluated regularly.”⁴⁹ Thus, the Lucentis label recognized the burdensome nature of monthly injections, but also that less frequent injections would not be effective.

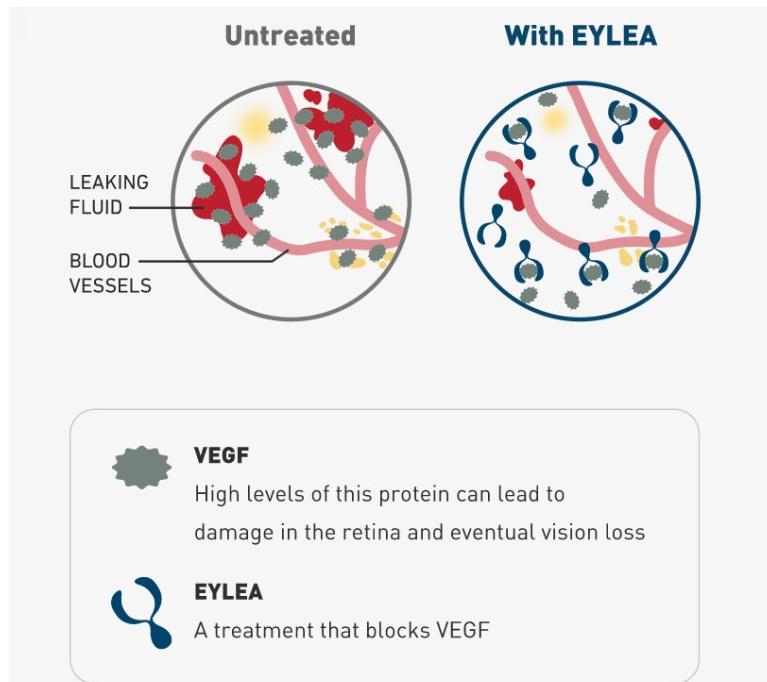
C. Eylea®

46. Through substantial development efforts in clinical trials, Regeneron achieved such an extended dosing regimen in conjunction with its anti-VEGF agent, Eylea®.

47. Eylea® (active ingredient afibercept) is an anti-VEGF agent that binds to VEGF in the eye. That is beneficial to patients with angiogenic eye disorders, who typically have overproduction of VEGF in the eye, which results in various pathologic changes in the eye. An image depicting Eylea’s® mechanism of action (binding VEGF) is shown below.⁵⁰ Eylea® was a completely novel type of anti-VEGF therapy. Unlike Macugen (an aptamer) or Lucentis (a Fab fragment of anti-VEGF antibody) Eylea® was an immunoadhesin that was completely genetically engineered to contain two VEGF receptors bound to the Fc portion of a human antibody.

⁴⁹ Lucentis Label (2006).

⁵⁰ Discover EYLEA, available at <https://www.eylea.us/s/how-eylea-works> (May 2022).



48. Despite the past failures of extended dosing regimens for anti-VEGF agents, Dr. Yancopoulos of Regeneron directed the testing of an extended regimen for Eylea® in the two phase 3 trials (VIEW 1 and VIEW 2) that ultimately led to its approval in 2011 for wet AMD.⁵¹ Thus, VIEW 1 and VIEW 2 both tested the efficacy of three monthly injections of 2 mg of aflibercept *followed by injections every eight weeks thereafter.*⁵² Given the uncertainty and skepticism surrounding extended dosing regimens, Regeneron also included a second regimen using 2 mg Eylea® in both the VIEW 1 and VIEW 2 studies—that regimen used the same monthly dosing regimen as Lucentis®, and never transitioned to extended, every-eight-week dosing.⁵³ In a third Eylea® arm, patients received 0.5 mg Eylea® every four weeks (*i.e.*,

⁵¹ See generally Heier (2012); see Yancopoulos Tr. 30:14–32:15, 105:4–106:13, 107:3–110:25.

⁵² See Yancopoulos Tr. 49:11–20.

⁵³ Yancopoulos Tr. 41:15–42:1, 176:18–177:16; see Heier (2012) at 2537.

monthly), and the control arm of the study was the standard of care Lucentis® treatment—0.5 mg Lucentis every month.⁵⁴

49. Remarkably, the results of VIEW 1 and VIEW 2 showed that the use of an eight-week dosing interval with Eylea® was just as effective as the shorter (*i.e.*, monthly) interval used with Lucentis® in patients with wet AMD. This discovery reflected a paradigm shift in treatment of AMD, because patients could now obtain the same vision benefits with fewer trips to the doctor and fewer injections—a great benefit to themselves, their caregivers, and their physicians.⁵⁵

50. Later, Regeneron investigated whether Eylea® could be used to treat DME on an extended regimen. Again, Regeneron innovated a novel, extended dosing regimen using Eylea® to treat patients with DME. In this regimen—which was included in Regeneron’s Phase 3 trials VIVID and VISTA—patients received five monthly doses of Eylea® before transitioning to every-other-month dosing. This regimen proved remarkably effective, and the clinical trials using this regimen resulted in Eylea®’s approval for treatment of DME in 2014.⁵⁶

51. Regeneron also investigated whether Eylea® could be used to treat DR on an extended regimen. Again, Regeneron innovated a novel, extended dosing regimen using Eylea® to treat patients with DR, and received approval for a regimen of five monthly doses followed by every-other-month dosing, as supported by the VIVID, VISTA, and PANORAMA studies. Eylea® was approved for treatment of DR in patients with DME in 2014, and for DR more generally in 2019.

⁵⁴ Yancopoulos Tr. 39:21–40:7.

⁵⁵ See generally Heier (2012).

⁵⁶ See generally Korobelnik (2014).

52. Eylea® was also approved for macular edema following central RVO in 2012 and for macular edema following branch RVO in 2014, each using monthly dosing.

V. YANCOPOULOS PATENTS

53. The Yancopoulos patents claim Dr. Yancopoulos's invention of methods of treatment for angiogenic eye disorders using extended dosing regimens of Eylea®. More particularly, the claims relate to a period of monthly dosing / dosing every four weeks (sometimes referred to as "Q4" dosing), followed by Eylea® administered every-other-month / dosing every eight weeks (sometimes referred to as "Q8" dosing). Certain claims are directed to particular indications (AMD, DME, DR in patients with DME, and DR), and/or their respective approved regimens (3 monthly doses for AMD vs. 5 monthly doses for DME, before transitioning to dosing after 8 weeks). Certain claims also require that physicians measure gains in visual acuity in the patients to whom they administer Eylea® on these extended regimens—these claims reflect the surprising effectiveness of Eylea® on a dosing regimen that placed far less burden on patients than other available treatment options. The asserted claims of the Yancopoulos patents contain many additional limitations, each of which I address where appropriate below.

VI. MYLAN'S INFRINGEMENT OF REGENERON'S YANCOPOULOS PATENTS

54. I am informed that in this case, Regeneron asserts that by marketing YESAFILI™, Mylan will induce infringement of claims 1–23 and 25–28 of the '572 patent and claims 5–9, 11–12, 15–17, 19, 21, 23–25, 27–28, and 31–33 the '601 patent. I refer to these claims collectively as the "Asserted Claims" throughout my report.

55. As I explain in detail below, it is my opinion that by marketing YESAFILI™, Mylan will induce infringement of each and every Asserted Claim of the Yancopoulos Patents.

A. Claim Construction

56. I am informed that the parties dispute the meaning of several claim terms as follows:

Claim Term	Regeneron's Proposed Construction and Intrinsic Evidence	Mylan's Proposed Construction and Intrinsic Evidence
Best Corrected Visual Acuity ('601 patent, claims 5-6, 15-16, 23-24, and 31-32; '572 patent, claims 2, 3, 8, 10, 17, 21, and 30)	the best visual acuity that can be achieved with the use of a corrective lens	Plain and ordinary meaning: <i>Best Corrected Visual Acuity (BCVA), measured in letters, a clinical trial endpoint / measurement</i>
formulated as an isotonic solution ('572 patent, claims 6, 12, 18, 22)	Plain and ordinary meaning in view of the claims and specification, which does not require the presence of glucose.	No construction needed. I am informed that Mylan has not supplied briefing about this argument.
"wherein exclusion criteria for the patient include" ('601 patent, claims 9, 17, 25, 33; '572 patent, claim 14)	The claim limitations are appropriately construed as: "assessing the patient for (1) active ocular inflammation; and (2) active ocular or periocular infection, and administering aflibercept to the patient on the basis of the foregoing assessment." The "patient" is not limited to a clinical trial subject. These limitations are not "printed matter" and the limitations are entitled to patentable weight.	The "exclusion criteria" represent informational content regarding the patient that is not functionally related to other claim elements, and therefore, should be considered "printed matter" that are accorded "no patentable weight." To the extent the Court determines that this term should be accorded patentable weight, it should be construed as follows: <i>"wherein exclusion criteria for the patient to be eligible in the clinical study of the said method for treating include"</i>

57. I address infringement under both Regeneron's and Mylan's proposed constructions where appropriate.

B. Person of Ordinary Skill in the Art

58. I understand that a number of my opinions must be rendered from the perspective of someone that the patent law refers to as the "personal of ordinary skill in the art" or "POSA," as of the date of the claimed invention. I am also informed that the earliest date of invention asserted by Mylan is January 2010. My opinions regarding infringement would not change if that date fell anywhere in the range of January 2010 to July 2013, when I am informed that the full specification of the Yancopoulos patents was filed in Application No. 13/940,370.

59. I have been informed that a POSA is a hypothetical person who may possess the skills, education, and experience of multiple individuals working together as a team. I have been informed that factors for determining the level of ordinary skill in the art may include one or more of the following: (1) the educational level of the inventor; (2) the type of problems encountered in the art; (3) prior art solutions to those problems; (4) the rapidity with which innovations are made; (5) the sophistication of the relevant technology; and (6) the educational level of workers active in the field.

60. In my opinion, the POSA relevant to the Yancopoulos patents is an ophthalmologist with experience in treating angiogenic eye disorders, including through the use of VEGF antagonists, and would have access to individuals with experience with intravitreal injection formulations.

61. I am very familiar with the level of knowledge a person with the credentials of the POSA would have had in 2010-2013. As an initial matter, I myself had at least those credentials at the relevant times. In addition, as I explain in Section I above, immediately before and during

that period I was actively treating patients for the angiogenic eye disorders relevant to these proceedings, and was also instructing and mentoring other physicians in the treatment of angiogenic eye disease, including physicians in residencies and fellowships, as well as junior (faculty member) attending physicians. As a result of this work, I have a very good understanding of the knowledge that a person with the credentials of the POSA would have had.

62. I am informed that in proceedings before the Patent Trial and Appeals Board concerning the '601 Patent, Mylan asserted that “[a] POSA here would have: (1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and (2) the ability to understand results and findings presented or published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in (i) developing treatments for angiogenic eye disorders (such as AMD), including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists.⁵⁷ My opinions in this report would not change if I adopted Mylan’s definition of the POSA.

C. Law of Infringement

63. I have been informed that a direct infringement analysis involves a two-step process for each claim in question. First, the claim must be construed (a process I understand the Court is undertaking consistent with the disputes outlined above). Second, the construed claim is compared to the accused method to determine whether it meets each and every limitation of the

⁵⁷ *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2022-01226, Paper 2 at 35-36 (PTAB 2022).

claim. If each and every limitation is literally met, then the accused method literally infringes the claim.

64. I have also been informed that a method may infringe a claim literally or under the doctrine of equivalents. I have been informed that even if, for example, a doctor does not literally infringe a claim, the doctor nonetheless infringes the claim under the doctrine of equivalents if (1) the differences between each claim limitation and the accused equivalent are insubstantial or (2) each claim limitation and the accused equivalent performs substantially the same function in substantially the same way to obtain the same result. I have been informed that infringement under the doctrine of equivalents is assessed on a claim limitation-by-limitation basis. I have been informed that Plaintiffs bear the burden to prove infringement by a preponderance of the evidence, meaning that a factual proposition is more likely than not.

65. I also have been informed that a party can be liable for inducing the direct infringement of another. Specifically, I understand that a party may be liable for induced infringement when that party (a) knowingly induced infringement and (b) possessed specific intent to encourage another's infringement. I understand that information that Mylan prepares, provides or publishes to practitioners who could use its product, including (upon marketing) its FDA-approved label,⁵⁸ presentations to clinicians,⁵⁹ among other information, as well as its internal communications and state of mind, may provide evidence of Mylan's specific intent.

⁵⁸ Mylan does not yet have an FDA-approved label, and I therefore base my opinions on the Mylan's proposed YESAFILI™ labeling. MYL-AFL-BLA1079688. Should Mylan's product and proposed labeling receive FDA approval, I understand its proposed label would be included with every vial of YESAFILI™ sold. *See, e.g.*, Barve Tr. at 71-72. I further expect the label would be made available on a Mylan (or eventually Biocon) website as is common practice, *see, e.g.*, <https://www.semgleehcp.com/> (Viatris insulin glargine-yfgn website), as well as the FDA's website.

⁵⁹ MYL-AFL0089404; MYL-AFL0089391.

D. Mylan Induces Infringement of the '572 Patent

66. I understand that Mylan is seeking FDA approval to make and sell its “biosimilar” or “interchangeable” version of aflibercept (aflibercept-jbv) under the trade name YESAFILI™, which is also referred to in various documents as M710 or MYL-1701P. In my opinion that sale would induce infringement of the Asserted Claims of the '572 Patent. The reasons I have reached this conclusion are set forth below.

1. The Asserted Claims of the '572 Patent

67. I am informed that Regeneron asserts claims 1–23 and 25–28 of the '572 Patent. The claims of the '572 patent are reproduced below, and the ones that I understand to be asserted are highlighted.

What is claimed is:

1. A method of treating an angiogenic eye disorder in a patient in need thereof comprising sequentially administering to the patient by intravitreal injection a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;
wherein each secondary dose is administered approximately 4 weeks following the immediately preceding dose; and
wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose;
wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose.
2. The method of claim 1 wherein the patient achieves a gain in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.
3. The method of claim 2 wherein the patient gains at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.
4. The method of claim 3 wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose.

5 17. The method of claim 16 wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.
10 18. The method of claim 17 wherein the aflibercept is formulated as an isotonic solution.
15 19. The method of claim 17 wherein the aflibercept is formulated with a non-ionic surfactant.
20 20. The method of claim 17 wherein the patient achieves a gain in visual acuity within 24 weeks following the initial dose.
25 21. The method of claim 16 wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.
22 22. The method of claim 21 wherein the aflibercept is formulated as an isotonic solution.
23 23. The method of claim 21 wherein the aflibercept is formulated with a nonionic surfactant.
24 24. The method of claim 15 wherein only two secondary doses are administered to the patient.
25 25. The method of claim 15 wherein four secondary doses are administered to the patient.

5. The method of claim 3 wherein only two secondary doses are administered to the patient.
6. The method of claim 3 wherein the afibercept is formulated as an isotonic solution.
7. The method of claim 3 wherein the afibercept is formulated with a nonionic surfactant.
8. The method of claim 2 wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.
9. The method of claim 8 wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose.
10. The method of claim 2 wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.
11. The method of claim 10 wherein only two secondary doses are administered to the patient.
12. The method of claim 10 wherein the afibercept is formulated as an isotonic solution.
13. The method of claim 10 wherein the afibercept is formulated with a nonionic surfactant.
14. The method of claim 1 wherein exclusion criteria for the patient include both of:
- (1) active ocular inflammation; and
 - (2) active ocular or periocular infection.
15. A method of treating diabetic macular edema in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of afibercept, followed by one or more secondary doses of 2 mg of afibercept, followed by one or more tertiary doses of 2 mg of afibercept;
- wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and
- wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose.
16. The method of claim 15 wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose.
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26. A method of treating age related macular degeneration in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of afibercept, followed by one or more secondary doses of 2 mg of afibercept, followed by one or more tertiary doses of 2 mg of afibercept;
- wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and
- wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose;
- wherein the method is as effective in achieving a gain in visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose.
27. The method of claim 26 wherein only two secondary doses are administered to the patient.
28. The method of claim 26 wherein the gain in visual acuity is measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.
29. A method of treating age-related macular degeneration in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of afibercept, followed by one or more secondary doses of 2 mg of afibercept, followed by one or more tertiary doses of 2 mg of afibercept;
- wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and
- wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose;
- wherein the method is as effective in maintaining visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose.
30. The method of claim 29 wherein maintenance of visual acuity means loss of less than 15 letters Best Corrected Visual Acuity (BCVA) as measured by using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

2. Mylan instructs and encourages physicians to use YESAFILIT™ in the same way they use Eylea®

68. Mylan intends to market YESAFILIT™ as a biosimilar to Eylea®.⁶⁰ According to

FDA, “[a] biosimilar is a biologic medication that is highly similar to and has no clinically

⁶⁰ Biosimilars at Viatris, Global Healthcare Gateway, available at https://www.viatris.com/-/media/project/common/viatris/pdf/ghg/2021_356_ghg-biosimilar_3822_final.pdf (“Biosimilars at Viatris”); Momenta and Mylan Announce Development Strategy for M710, a Proposed

meaningful differences from an existing FDA-approved biologic, called a reference product.”⁶¹

FDA further explains that:

Compared with a reference product, biosimilars:

- Are made with the same types of living sources,
- Are given to the patient in the same way
- Have the same strength, dosage potential treatment benefits, and potential side effects.⁶²

69. Mylan’s proposed labeling for YESAFILI™, if approved, will also instruct physicians that YESAFILI™ is a biosimilar “interchangeable” with Eylea®. My understanding is that “interchangeable” is a particular designation for its proposed biosimilar product that Mylan has decided to seek.⁶³ According to FDA: “All FDA-approved biosimilars, including interchangeable biosimilars, must be highly similar to and have no clinically meaningful differences from the reference product in terms of safety and effectiveness. An interchangeable biosimilar is a biosimilar that meets additional requirements. A pharmacist may substitute an interchangeable biosimilar for its reference product without consulting the prescriber, depending

Biosimilar to EYLEA®(afibercept), Mylan (Jan. 3, 2018), available at <https://investor.mylan.com/news-releases/news-release-details/momenta-and-mylan-announce-development-strategy-m710-proposed> (“Jan. 2018 Mylan News Release”); MYL-AFL-BLA1079688, at -1079688.

⁶¹ *Overview for Health Care Professionals*, U.S. Food & Drug Administration (Dec. 13, 2022), available at <https://www.fda.gov/drugs/biosimilars/overview-health-care-professionals#What%20is%20a%20biosimilar%20product> (“FDA Biosimilar Definition”).

⁶² FDA Biosimilar Definition, *supra* note 61.

⁶³ MYL-AFL-BLA1079688, at -1079688.

on state pharmacy laws.”⁶⁴ According to FDA, “[f]or approval as an interchangeable biosimilar, manufacturers must provide additional data that reflect how the interchangeable biosimilar may be used in the marketplace with patients.”⁶⁵ In particular, “[i]n addition to establishing biosimilarity, a manufacturer of an interchangeable biosimilar needs to submit information to show that the proposed product can be expected to produce the same clinical result as the reference product in any given patient.”⁶⁶

70. Mylan’s proposed label for YESAFILI™ states that “YESAFILI™ (aflibercept-jbvf) is interchangeable* with EYLEA (aflibercept)” and continues, at the asterisked footnote, to explain that:

An interchangeable product (IP) is a biological product that is approved based on data demonstrating that it is highly similar to an FDA-approved reference product (RP) and that there are no clinically meaningful differences between the products; it can be expected to produce the same clinical result as the RP in any given patient; and if administered more than once to a patient, the risk in terms of safety or diminished efficacy from alternating or switching between the use of the RP and IP is not greater than that from the PR without such alternation or switch . Interchangeability of YESAFILI has been demonstrated for the condition(s) of use, strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.⁶⁷

⁶⁴ FDA Biosimilar Definition, *supra* note 61.

⁶⁵ *Interchangeable Biological Products*, U.S. Food & Drug Administration, available at <https://www.fda.gov/media/151094/download> (“Interchangeable Biological Products”).

⁶⁶ *Review and Approval*, U.S. Food and Drug Administration (Dec. 13, 2022), available at <https://www.fda.gov/drugs/biosimilars/review-and-approval#interchangeable%20biosimilar%20products> (“Data Requirements for Interchangeable Biosimilar Products”).

⁶⁷ MYL-AFL-BLA1079688, at -1079688.

The FDA guidance Mylan consulted in preparing its label⁶⁸ makes clear that such language was recommended to be included in interchangeable biosimilar labels, but not required.⁶⁹ Mylan has made an affirmative decision to seek FDA approval of a label containing this language.

71. In this way, Mylan's proposed labeling conveys that YESAFILI™ can and should be administered in the same way as Eylea®. Indeed, Mylan's proposed labeling for YESAFILI™ is nearly identical to Eylea's® currently approved label.⁷⁰ I have included below images showing Eylea's® Highlights of Prescribing Information as compared with YESAFILI's™ proposed Highlights of Prescribing Information.⁷¹ I have highlighted differences not due to name and approval dates/history below in red (Eylea®) and yellow (YESAFILI™).⁷²

⁶⁸ MYL-AFL-BLA1077647, at -1077647 (comments indicating “[t]ext revised in accordance with the Agency’s Guidance, *Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act* (November 2020)”; Niesner Tr. at 115:16-116:12.

⁶⁹ U.S. Department of Health and Human Services et al., *Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act* (November 2020), available at <https://www.fda.gov/media/143847/download> (“Biosimilarity and Interchangeability Draft Guidance”), at 2 (“In general, FDA’s guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.”), 9 (“FDA *recommends* including a statement, placed on the line immediately beneath the Initial U.S. Approval in the Highlights of Prescribing Information (Highlights), that the product is interchangeable with the reference product. It *should* read as follows The asterisk *should* appear as a footnote symbol inserted after the word “interchangeable.” . . . The footnote *should* appear, in regular (not bold) font, at the end of Highlights (but above the Revision Date) and state the following” (emphases added)).

⁷⁰ Compare MYL-AFL-BLA1079688 (YESAFILI™ Label) with Eylea® Label (2022).

⁷¹ MYL-AFL-BLA1079688, at -1079688; Eylea® Label (2022), at 1.

⁷² MYL-AFL-BLA1079688, at -1079688; Eylea® Label (2022), at 1.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EYLEA safely and effectively. See full prescribing information for EYLEA.

EYLEA® (afiblervcept) Injection, for intravitreal use

Initial U.S. Approval: 2011

RECENT MAJOR CHANGES

Dosage and Administration (2.6, 2.8) 8/2022

INDICATIONS AND USAGE

EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1.2)
- Diabetic Macular Edema (DME) (1.3)
- Diabetic Retinopathy (DR) (1.4)

DOSAGE AND ADMINISTRATION

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.2)
- Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months). (2.2)
- Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly. (2.2)

Macular Edema Following Retinal Vein Occlusion (RVO)

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly). (2.3)

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.4, 2.5)
- Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months). (2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

- **Injection: 2 mg/0.05 mL solution in a single-dose pre-filled syringe (3)**
- Injection: 2 mg/0.05 mL solution in a single-dose vial (3)

CONTRAINdications

- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

WARNINGS AND PRECAUTIONS

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. (5.3)

ADVERSE REACTIONS

The most common adverse reactions ($\geq 5\%$) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-855-395-3248 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 8/2022

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use YESAFILI safely and effectively. See full prescribing information for YESAFILI.

YESAFILI™ (afibbercept-jbv) Injection, for intravitreal use

Initial U.S. Approval: 20XX

YESAFILI™ (afibbercept-jbv) is interchangeable* with EYLEA (afibbercept).

INDICATIONS AND USAGE

YESAFILI is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1.2)
- Diabetic Macular Edema (DME) (1.3)
- Diabetic Retinopathy (DR) (1.4)

DOSAGE AND ADMINISTRATION

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

- The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.2)
- Although YESAFILI may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when afibbercept was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months). (2.2)
- Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly. (2.2)

Macular Edema Following Retinal Vein Occlusion (RVO)

- The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly). (2.3)

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)

- The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.4, 2.5)
- Although YESAFILI may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when afibbercept was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months). (2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

- Injection: 2 mg/0.05 mL solution in a single-dose vial (3)

CONTRAINDICATIONS

- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

WARNINGS AND PRECAUTIONS

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. (5.3)

ADVERSE REACTIONS

The most common adverse reactions ($\geq 5\%$) reported in patients receiving afibbercept were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

* An interchangeable product (IP) is a biological product that is approved based on data demonstrating that it is highly similar to an FDA-approved reference product (RP) and that there are no clinically meaningful differences between the products; it can be expected to produce the same clinical result as the RP in any given patient; and if administered more than once to a patient, the risk in terms of safety or diminished efficacy from alternating or switching between use of the RP and IP is not greater than that from the RP without such alternation or switch. Interchangeability of YESAFILI has been demonstrated for the condition(s) of use, strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

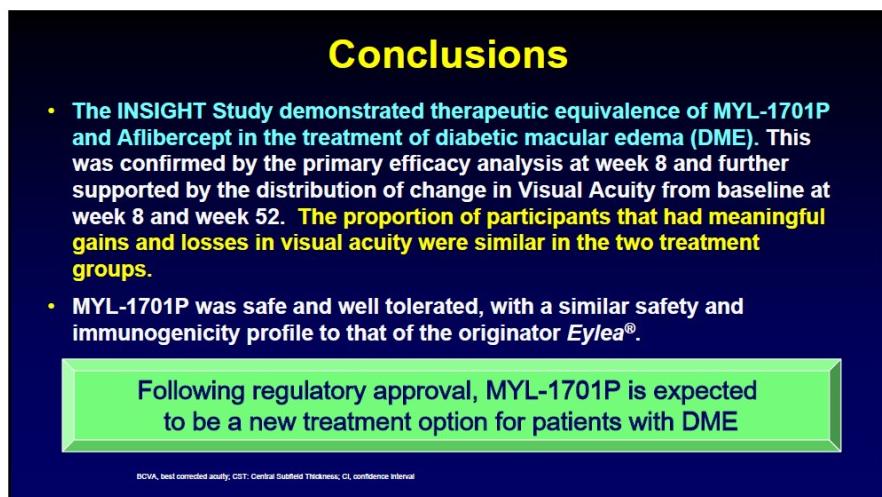
Revised: 8/2022

72. Mylan and its clinical trial investigators also have presented at various conferences (including the American Academy of Ophthalmology's annual meeting ("AAO")) the results of the single Phase III study it conducted to compare YESAFILI™ to Eylea®, in patients with DME.⁷³ In those presentations, Mylan explained that patients were "randomly assigned to the proposed biosimilar or the originator biologic *with the dosing and treatment regimen in the originator's label*" and touted that "the change in visual acuity from baseline was virtually the same in the MYL-1701P and afibbercept arms."⁷⁴ Mylan broadcasted its results to

⁷³ MYL-AFL0089404; MYL-AFL0089391.

⁷⁴ MYL-AFL089404, at -089407, -089411.

physicians, stating that their data showed “therapeutic equivalence” and “clinical equivalence” between YESAFILIT™ and Eylea®.⁷⁵ For example, Dr. Susan Bressler—an ophthalmologist with the Wilmer Eye Institute at Johns Hopkins—presented Mylan’s clinical trial results at AAO 2022,⁷⁶ including the following slide that specifically encourages physicians to use YESAFILIT™ in the same manner as Eylea®, and further directs physicians to use YESAFILIT™ to treat DME:⁷⁷



73. Mylan’s presentation at AAO 2022 accompanied a poster presentation.⁷⁸ Mylan’s presentation at the 2022 conference of the American Society of Retinal Specialists appears to

⁷⁵ MYL-AFL0089391, at -089397, -089401 to -089403.

⁷⁶ MYL-AFL0089391 at -0089391; Ganapathi Tr. at 159:9-70:7. Mylan’s rationale in selecting DME for their study was because they believe the mechanism of action is “representative of the mechanism of action of Eylea in all other indications for which Eylea is approved.” MYL-AFL-BLA0552833, at -0552833. This supports the point that Mylan’s DME trial induces infringement as to AMD.

⁷⁷ MYL-AFL0089391, at -0089402.

⁷⁸ MYL-AFL0089391 at -0089391 (referencing PO387); Ganapathi Tr. at 162:8-21; Skylar Jeremias, *Positive Results for Aflibercept Biosimilars Seen at AAO 2022*, AJMC: The Center for

have been a standalone oral presentation.⁷⁹ In both instances, Mylan's consultant, Dr. Bressler presented on behalf of a number of co-authors, including Mylan employees in charge of various aspects of YESAFILI™ clinical development.⁸⁰ Mylan employees seem to have reviewed both these presentations before they were delivered,⁸¹ which is consistent with my experience in the industry. These presentations described biosimilars as "alternatives" to their reference product biologics,⁸² and described YESAFILI™ as comparable and similar to Eylea®⁸³ and "equivalen[t]" in terms of efficacy.⁸⁴

74. I have attended the annual conferences of both ASRS and AAO many times over my decades in the field. These conferences, like most held by the major ophthalmology professional societies, are attended primarily by clinicians like myself seeking to connect with

Biosimilars (Oct. 5, 2022), available at <https://www.centerforbiosimilars.com/view/positive-results-for-aflibercept-biosimilars-seen-at-ao-2022> ("Jeremias").

⁷⁹ Ganapathi Tr. at 164:13-22.

⁸⁰ MYL-AFL0089391 (listing as co-authors Abhijit Barve (Viatris Chief Medical Officer and member of the Mylan-Momenta Joint Steering Committee overseeing M710), Katrin Beckman (Mylan statistician for DME study), Annalakshmi Jagatheesan (Mylan Clinical Sciences Study Lead- Clinical R&D and a member of the Mylan Clinical Sciences Team with responsibility for the DME trial), and Prasanna Ganapathi (Mylan Clinical Sciences Program Lead and Mylan's Medical Officer responsible for the DME trial)); MYL-AFL0089404 (also listing as co-authors Abhijit Barve, Katrin Beckman, Annalakshmi Jagatheesan, and Prasanna Ganapathi).

⁸¹ Ganapathi Tr. at 163:13-64:12. I also have been informed both presentations were produced from the files of Mylan Pharmaceuticals, Inc. and that metadata reveals the file name of the ASRS presentation is "final ASRS 2022 draft 13Jul22_Clean Version_with Viatris final edits.pptx."

⁸² MYL-AFL0089391, at -0089393; MYL-AFL0089404, at -0089406.

⁸³ MYL-AFL0089391; MYL-AFL0089404.

⁸⁴ MYL-AFL0089391, at -0089402; MYL-AFL0089404, at -0089418.

colleagues and stay up to date on the most current treatment techniques and strategies.

Pharmaceutical companies working to bring new drugs to market or expand the reach of their current products frequently present at such conferences to share their findings and educate the medical community, including the prescribing and treating physicians who will eventually use their medicines.⁸⁵

75. In other words, Mylan presented the results of its study in a manner that will encourage physicians to administer YESAFILI™ in precisely the same way they administer Eylea®, and that recommends and promotes to them that they do so. It is difficult to view such presentations as anything other than reflecting an intent to encourage and recommend to physicians that they administer YESAFILI™ in the same way they administer Eylea®. I understand that Regeneron has asked Mylan to identify any differences in how it intended physicians to use YESAFILI™ compared to Eylea®, and that Mylan declined to answer and did not identify any such differences.⁸⁶

76. Mylan's presentations about and marketing of YESAFILI™ as an effectively identical product with dosing and administration labeling instructions effectively the same as those for Eylea® naturally will induce ophthalmologists to use and administer YESAFILI™ in the same manner that they have used and administered Eylea® for years.⁸⁷ Ophthalmologists

⁸⁵ See Barve Tr. at 100:16-101:8 (“Q. In your experience, what’s the purpose of presenting presentations like the two that we’re looking at, [the YESAFILI ASRS and AAO presentations] to be clear? . . . A. Share the results of the studies. Q. With whom? A. With the intended audience. Q. And who is the intended audience? . . . A. In which case? Q. These medical conferences? A. The doctors who are attending the conference.”).

⁸⁶ See Mylan Pharmaceuticals Inc.’s Answers & Objs. to Regeneron’s Fourth Set of Interrogs. at 17-18 (Jan. 18, 2023).

⁸⁷ See Barve Tr. 58:15–21 (Q. Who’s the intended audience for prescribing information? A. Prescribers. Q. Doctors? A. That prescribe the product. Q. So medical doctors, right? A. Yes.”).

who are administering treatments to AMD, DME, RVO, or DR patients are not in a position to evaluate the safety and efficacy of generic or biosimilar products. Mylan's statements that there are no clinically meaningful differences and instructs that its biosimilar or interchangeable product is "highly similar" to a reference product, "can be expected to produce the same clinical result as the [reference product] in any given patient," and should be used in the same way in treating patients will be accorded significant weight by physicians.

77. Mylan's message that YESAFILI™ should be used in the same way as Eylea® matters because ophthalmologists have administered Eylea®—consistent with Regeneron's instructions—in a manner that practices the Asserted Claims.

3. Mylan Induces Infringement of Claim 1 of the '572 Patent

78. Claim 1 of the '572 patent contains five limitations, each of which I address in turn below:

- (1pre) A method of treating an angiogenic eye disorder in a patient in need thereof comprising
- (1a) sequentially administering to the patient by intravitreal injection a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;
- (1b) wherein each secondary dose is administered approximately 4 weeks following the immediately preceding dose; and
- (1c) wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose;
- (1d) wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose.

79. By marketing YESAFILI™ in accordance with its proposed labeling, Mylan knows and specifically intends that physicians will perform every limitation of the method of claim 1. I explain the basis for my opinion in further detail below, and in the claim charts appended to this report at Appendix C. I hereby incorporate by reference my analysis in those claim charts as though set forth fully herein.

a) (1pre) “A method of treating an angiogenic eye disorder in a patient in need thereof comprising”

80. With respect to the first limitation (also called the preamble)—“A method of treating an angiogenic eye disorder in a patient in need thereof comprising”—it is standard Eylea® clinical practice, as exemplified by the Eylea® label, to administer Eylea® to patients in need of treatment for various angiogenic eye disorders, in order to treat those angiogenic eye disorders.⁸⁸ Specifically, the Eylea® label instructs physicians to administer aflibercept to treat the following diseases:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)

Each of these diseases is an angiogenic eye disorder.⁸⁹ A physician administering YESAFILI™ in the same manner (and as “interchangeable* with EYLEA (aflibercept)”) would meet this limitation.

⁸⁸ Eylea Label (2022) at 1-2.

⁸⁹ *Supra* Section IV.A.

81. Further, Mylan's proposed YESAFILI™ labeling instructs physicians to administer YESAFILI™ to treat various angiogenic eye disorders.⁹⁰ Specifically, Mylan's proposed labeling for YESAFILI™ expressly instructs physicians to administer YESAFILI™ to treat the following diseases:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)⁹¹

Again, each of these diseases is an angiogenic eye disorder.⁹²

82. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform limitation (1pre). In other words, if Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will administer YESAFILI™ to treat angiogenic eye disorders, including AMD, RVO, DME, and/or DR.

83. Mylan's proposed labeling encourages, recommends, and promotes performance of limitation (1pre) by physicians. Indeed, by marketing YESAFILI™ with its proposed

⁹⁰ MYL-AFL-BLA1079688 at -1079688; MYL-AFL-BLA1079688 at -1079688; MYL-AFL-BLA1079688 at -1079700, at section 12.1 (“Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PIGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PIGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PIGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.”); *supra* Section IV.A.

⁹¹ MYL-AFL-BLA1079688 at Highlights of Prescribing Information; MYL-AFL-BLA1079688 at Highlights of Prescribing Information.

⁹² *Supra* Section IV.A.

labeling, Mylan knows that physicians will administer YESAFILI™ to treat angiogenic eye disorders in a manner consistent with Claim 1 of the '572 Patent, and specifically intends this infringing activity.

84. I incorporate by reference my analysis of this limitation in the claim charts appended hereto as Appendix C as though set forth fully herein.

- b) (1a) **“sequentially administering to the patient by intravitreal injection a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept”**

85. The second limitation of claim 1 requires that the physician “sequentially administer to the patient by intravitreal injection a single initial dose of 2 mg of aflibercept” followed by one or more “secondary” doses of 2 mg of aflibercept, followed by one or more “tertiary” doses of 2 mg of aflibercept. It is standard Eylea® clinical practice, as exemplified by the Eylea® label, to administer an “initial” dose of 2 mg Eylea® (aflibercept), followed by one or more “secondary” doses of 2 mg Eylea® (aflibercept), followed by one or more “tertiary” doses of 2 mg Eylea® (aflibercept).⁹³

86. Specifically, the Eylea® label instructs physicians to treat the angiogenic eye disorder of AMD by administering 2 mg of Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”⁹⁴

87. Accordingly, the Eylea® label instructs physicians to treat the angiogenic eye disorder AMD by administering a single “initial” dose of 2 mg aflibercept, followed by a

⁹³ Eylea® Label (2022) at 1-2.

⁹⁴ Eylea® Label (2022) at 1-2.

“secondary” dose of 2 mg Eylea® (aflibercept) four weeks later, followed by another “secondary” dose of 2 mg Eylea® (aflibercept) four weeks after that, followed by a tertiary dose of 2 mg Eylea® (aflibercept) eight weeks after that (*i.e.*, eight weeks after the second, “secondary” dose), followed by additional “tertiary” doses of 2 mg Eylea® at 8 week intervals thereafter.⁹⁵

88. In other words, when the Eylea® label instructs a physician to administer 2 mg Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months”, it expressly instructs physicians to administer “a single initial dose of 2 mg of aflibercept, followed by [two] secondary doses of 2 mg of aflibercept.” When the Eylea® label instructs a physician that the first three monthly doses should be “followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months),” the Eylea® label expressly instructs physicians to administer “one or more tertiary doses of 2 mg of aflibercept.”

89. A physician practicing the dosing regimen instructed by Eylea’s® label for the treatment of AMD would meet this limitation of claim 1, and a physician administering YESAFILI™ in the same manner would also meet this limitation.

90. Similarly, the Eylea® label instructs physicians to treat the angiogenic eye disorders of DME and DR by administering 2 mg of Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”⁹⁶

⁹⁵ Eylea® Label (2022) at 1-2.

⁹⁶ Eylea® Label (2022) at 1-2.

91. Accordingly, the Eylea® label instructs physicians to treat the angiogenic eye disorders DME and DR by administering a single “initial” dose of 2 mg aflibercept, followed by a “secondary” dose of 2 mg Eylea® (aflibercept) four weeks later, followed by another “secondary” dose of 2 mg Eylea® (aflibercept) four weeks after that, followed by a third “secondary” dose of 2 mg Eylea® (aflibercept) four weeks after that, followed by a fourth “secondary” dose of 2 mg Eylea® (aflibercept) four weeks after that, followed by a “tertiary” dose of 2 mg Eylea® (aflibercept) eight weeks after that (*i.e.*, eight weeks after the fourth, “secondary” dose), followed by additional “tertiary” doses of 2 mg Eylea® at 8 week intervals thereafter.

92. In other words, because the Eylea® label instructs a physician to administer 2 mg Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections”, it expressly instructs physicians to administer “a single initial dose of 2 mg of aflibercept, followed by [four] secondary doses of 2 mg of aflibercept.” Because the Eylea® label instructs a physician that the first five injections should be “followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months),” the Eylea® label expressly instructs physicians to administer “one or more tertiary doses of 2 mg of aflibercept.”

93. A physician practicing the dosing regimen instructed by Eylea’s® label for the treatment of DME and/or DR would meet this limitation of claim 1, and physician administering YESAFILI™ in the same manner would also meet this limitation.

94. Further, Mylan’s proposed YESAFILI™ labeling instructs physicians to administer YESAFILI™ to treat AMD, DME, and DR using precisely the same regimens contained in Eylea’s® label.⁹⁷

⁹⁷ MYL-AFL-BLA1079688, at -1079688 to -1079689.

95. Specifically, Mylan's proposed YESAFILI™ labeling instructs physicians to treat the angiogenic eye disorder of AMD by administering 2 mg of YESAFILI™ (aflibercept) "by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)."

96. Accordingly, Mylan's proposed YESAFILI™ labeling instructs physicians to treat the angiogenic eye disorders of AMD by administering a single "initial" dose of 2 mg aflibercept, followed by a "secondary" dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks later, followed by another "secondary" dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks after that, followed by a tertiary dose of 2 mg YESAFILI™ (aflibercept-jbvf) eight weeks after that (*i.e.*, eight weeks after the second, "secondary" dose), followed by additional "tertiary" doses of 2 mg YESAFILI™ (aflibercept-jbvf) at 8 week intervals thereafter.

97. In other words, because the YESAFILI™ label instructs a physician to administer 2 mg YESAFILI™ (aflibercept-jbvf) "by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months", it expressly encourages, recommends, and promotes physicians to administer "a single initial dose of 2 mg of aflibercept, followed by [two] secondary doses of 2 mg of aflibercept." Because the YESAFILI™ label instructs a physician that the first three monthly doses should be "followed by 2 mg (0.05 mL) [YESAFILI™(aflibercept-jbvf)] via intravitreal injection once every 8 weeks (2 months)," the YESAFILI™ label expressly encourages, recommends, and promotes physicians to administer "one or more tertiary doses of 2 mg of aflibercept."

98. Similarly, Mylan's proposed YESAFILI™ labeling instructs physicians to treat the angiogenic eye disorder of DME and DR by administering 2 mg of YESAFILI™ (aflibercept-jbvf) "by intravitreal injection every 4 weeks (approximately every 28 days,

monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”⁹⁸

99. Accordingly, the YESAFILI™ label instructs physicians to treat the angiogenic eye disorders DME and DR by administering a single “initial” dose of 2 mg aflibercept, followed by a “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks later, followed by another “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks after that, followed by a third “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks after that, followed by a fourth “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks after that, followed by a “tertiary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) eight weeks after that (*i.e.*, eight weeks after the fourth, “secondary” dose), followed by additional “tertiary” doses of 2 mg YESAFILI™ at 8 week intervals thereafter.

100. In other words, because the YESAFILI™ label instructs a physician to administer 2 mg YESAFILI™ (aflibercept-jbvf) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections”, it expressly encourages, recommends, and promotes physicians to sequentially administer “a single initial dose of 2 mg of aflibercept, followed by [four] secondary doses of 2 mg of aflibercept.” When the YESAFILI™ label instructs a physician that the first five injections should be “followed by 2 mg (0.05 mL) [YESAFILI™(aflibercept-jbvf)] via intravitreal injection once every 8 weeks (2 months),” the YESAFILI™ label expressly encourages, recommends, and promotes physicians to sequentially administer “one or more tertiary doses of 2 mg of aflibercept.”⁹⁹

⁹⁸ MYL-AFL-BLA1079688, at -1079688 to -1079689.

⁹⁹ MYL-AFL-BLA1079688 at -1079688 to -1079689.

101. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform limitation (1a). In other words, if Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will sequentially administer to the patient by intravitreal injection a single initial dose of 2 mg of YESAFILI™ (aflibercept-jbvf), followed by one or more secondary doses of 2 mg of YESAFILI™ (aflibercept-jbvf), followed by one or more tertiary doses of 2 mg of YESAFILI™ (aflibercept-jbvf).

102. Mylan's proposed labeling encourages, recommends, and promotes performance of limitation (1a) by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will sequentially administer to the patient by intravitreal injection a single initial dose of 2 mg of YESAFILI™ (aflibercept-jbvf), followed by one or more secondary doses of 2 mg of YESAFILI™ (aflibercept-jbvf), followed by one or more tertiary doses of 2 mg of YESAFILI™ (aflibercept-jbvf).

103. I also incorporate by reference my analysis of this limitation in the claim charts appended hereto as Appendix C as though set forth fully herein.

c) (1b) “wherein each secondary dose is administered approximately 4 weeks following the immediately preceding dose;”

104. Limitation (1b) requires that the physician administer the doses described in limitation (1a), “wherein each secondary dose is administered approximately four weeks following the immediately preceding dose.” It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to administer an “initial” dose of 2 mg Eylea® (aflibercept), followed by two (for the treatment of AMD) or four (for the treatment of DME and for the

treatment of DR) “secondary” doses of 2 mg Eylea® (aflibercept) “approximately four weeks following the immediately preceding dose.”¹⁰⁰

105. Specifically, the Eylea® label instructs physicians to treat the angiogenic eye disorder of AMD by administering 2 mg of Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”¹⁰¹ As I described above in connection with limitation (1a)—an analysis I incorporate herein by reference—this instruction directs physicians to administer one initial dose of 2 mg Eylea®, followed by a first “secondary” dose of 2 mg Eylea® four weeks later, followed by a second “secondary” dose of 2 mg Eylea® four weeks after that, before transitioning to the administration of tertiary doses. Thus, the Eylea® label expressly instructs physicians to administer an initial dose of 2 mg Eylea®, followed by two secondary doses “wherein each secondary dose is administered approximately four weeks following the immediately preceding dose.”

106. A physician practicing the dosing regimen instructed by Eylea’s® label for the treatment of AMD would meet this limitation of claim 1, and physician administering YESAFILI™ in the same manner would also meet this limitation.

107. Similarly, the Eylea® label instructs physicians to treat the angiogenic eye disorders of DME and DR by administering 2 mg of Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”¹⁰² As I

¹⁰⁰ Eylea® Label (2022) at 1-2.

¹⁰¹ Eylea® Label (2022) at 1-2.

¹⁰² Eylea® Label (2022) at 1-2.

described above in connection with limitation (1a)—an analysis I incorporate herein by reference—this instruction directs physicians to administer one initial dose of 2 mg Eylea®, followed by a first “secondary” dose of 2 mg Eylea® four weeks later, followed by a second “secondary” dose of 2 mg Eylea® four weeks after that, followed by a third “secondary” dose of 2 mg Eylea® four weeks after that, followed by a fourth “secondary” dose of 2 mg Eylea® four weeks after that, before transitioning to the administration of tertiary doses. Thus, the Eylea® label expressly instructs physicians to administer an initial dose of 2 mg Eylea®, followed by four secondary doses “wherein each secondary dose is administered approximately four weeks following the immediately preceding dose.”¹⁰³

108. A physician practicing the dosing regimen instructed by Eylea’s® label for the treatment of AMD would meet this limitation of claim 1, and a physician administering YESAFILI™ in the same manner would also meet this limitation.

109. Further, Mylan’s proposed labeling for YESAFILI™ instructs physicians to treat the angiogenic eye disorder of AMD by administering 2 mg of YESAFILI™ (afibercept-jbvf) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”¹⁰⁴ As I described above in connection with limitation (1a)—an analysis I incorporate herein by reference—this instruction directs physicians to administer one initial dose of 2 mg YESAFILI™ (afibercept-jbvf), followed by a first “secondary” dose of 2 mg YESAFILI™ (afibercept-jbvf) four weeks later, followed by a second, “secondary” dose of 2 mg YESAFILI™ (afibercept-jbvf) four weeks after that, before transitioning to the administration

¹⁰³ Eylea® Label (2022) at 1-2.

¹⁰⁴ MYL-AFL-BLA1079688 at -1079688 to -1079689.

of tertiary doses. Thus, the YESAFILI™ label expressly encourages, recommends, and promotes physicians to administer an initial dose of 2 mg YESAFILI™ (aflibercept-jbvf), followed by two secondary doses of YESAFILI™ (aflibercept-jbvf), “wherein each secondary dose is administered approximately four weeks following the immediately preceding dose,” in order to treat AMD.

110. Similarly, the YESAFILI™ label instructs physicians to treat the angiogenic eye disorders of DME and DR by administering 2 mg of YESAFILI™ (aflibercept-jbvf) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”¹⁰⁵ As I described above in connection with limitation (1a)—an analysis I incorporate herein by reference—this instruction directs physicians to administer one initial dose of 2 mg YESAFILI™ (aflibercept-jbvf), followed by a first “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks later, followed by a second “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks after that, followed by a third “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks after that, followed by a fourth “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks after that, before transitioning to the administration of tertiary doses. Thus, the YESAFILI™ label expressly encourages, recommends, and promotes physicians to administer an initial dose of 2 mg YESAFILI™ (aflibercept-jbvf), followed by four secondary doses “wherein each secondary dose is administered approximately four weeks following the immediately preceding dose,” in order to treat DME and in order to treat DR.¹⁰⁶

¹⁰⁵ MYL-AFL-BLA1079688 at -1079688 to -1079689.

¹⁰⁶ MYL-AFL-BLA1079688 at -1079688 to -1079689.

111. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform limitation (1b). In other words, if Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will administer YESAFILI™ such that each secondary dose is administered approximately 4 weeks following the immediately preceding dose.

112. Mylan's proposed labeling encourages, recommends, and promotes performance of limitation (1b) by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will administer YESAFILI™ to treat angiogenic eye disorders in a manner consistent with Claim 1 of the '572 Patent, and specifically intends this infringing activity.

113. I also incorporate by reference my analysis of this limitation in the claim charts appended hereto as Appendix C as though set forth fully herein.

d) (1c) “wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose”

114. Limitation (1c) requires that the physician administer the doses described in limitation (1a), “wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose.” It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to administer an “initial” dose of 2 mg Eylea® (aflibercept), followed by two (for the treatment of AMD) or four (for the treatment of DME and DR) “secondary” doses of 2 mg Eylea®, followed by one or more tertiary doses that are “administered approximately 8 weeks following the immediately preceding dose.”

115. Specifically, the Eylea® label instructs physicians to treat the angiogenic eye disorder of AMD by administering 2 mg of Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months, followed by 2 mg

(0.05 mL) via intravitreal injection once every 8 weeks (2 months).”¹⁰⁷ As I described above in connection with limitation (1a)—an analysis I incorporate herein by reference—this instruction directs physicians to treat the angiogenic eye disorder AMD by administering a single “initial” dose of 2 mg aflibercept, followed by a “secondary” dose of 2 mg Eylea® (aflibercept) four weeks later, followed by another “secondary” dose of 2 mg Eylea® (aflibercept) four weeks after that, followed by a “tertiary” dose of 2 mg Eylea® (aflibercept) eight weeks after that (*i.e.*, eight weeks after the second, “secondary” dose), followed by additional “tertiary” doses of 2 mg Eylea at 8 week intervals thereafter. Accordingly, the Eylea® label instructs physicians to administer one or more tertiary doses “wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose.”¹⁰⁸

116. A physician practicing the dosing regimen instructed by Eylea’s® label for the treatment of AMD would meet this limitation of claim 1, and physician administering YESAFILI™ in the same manner would also meet this limitation.

117. Similarly, the Eylea® label instructs physicians to treat the angiogenic eye disorders of DME and DR by administering 2 mg of Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”¹⁰⁹ As I described above in connection with limitation (1a)—an analysis I incorporate herein by reference—this instruction directs physicians to administer one initial dose of 2 mg Eylea®, followed by a first “secondary” dose of 2 mg Eylea® four weeks later, followed by a second

¹⁰⁷ Eylea® Label (2022) at 1-2.

¹⁰⁸ Eylea® Label (2022) at 1-2.

¹⁰⁹ Eylea® Label (2022) at 1-2.

“secondary” dose of 2 mg Eylea® four weeks after that, followed by a third “secondary” dose of 2 mg Eylea® four weeks after that, followed by a fourth “secondary” dose of 2 mg Eylea® four weeks after that, followed by a “tertiary” dose of 2 mg Eylea® (afibercept) eight weeks after that (*i.e.*, eight weeks after the fourth “secondary” dose), followed by additional “tertiary” doses of 2 mg Eylea® at 8 week intervals thereafter. Thus, the Eylea® label expressly instructs physicians to administer one or more tertiary doses “wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose.”¹¹⁰

118. A physician practicing the dosing regimen instructed by Eylea’s® label for the treatment of DME and/or for the treatment of DR would meet this limitation of claim 1, and physician administering YESAFILI™ in the same manner would also meet this limitation.

119. Further, Mylan’s proposed labeling for YESAFILI™ instructs physicians to treat the angiogenic eye disorder of AMD by administering 2 mg of YESAFILI™ (afibercept-jbvf) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”¹¹¹ As I described above in connection with limitation (1a)—an analysis I incorporate herein by reference—this instruction directs physicians to treat the angiogenic eye disorder AMD by administering a single “initial” dose of 2 mg YESAFILI™ (afibercept-jbvf), followed by a “secondary” dose of 2 mg YESAFILI™ (afibercept-jbvf) four weeks later, followed by another “secondary” dose of 2 mg YESAFILI™ (afibercept-jbvf) four weeks after that, followed by a “tertiary” dose of 2 mg YESAFILI™ (afibercept-jbvf) eight weeks after that (*i.e.*, eight weeks after the second, “secondary” dose), followed by additional “tertiary” doses of 2 mg

¹¹⁰ Eylea Label® (2022) at 1-2.

¹¹¹ MYL-AFL-BLA1079688 at -1079688 to -1079689.

YESAFILI™ (aflibercept-jbvf) at 8 week intervals thereafter. Thus, the YESAFILI™ label expressly encourages, recommends, and promotes physicians to administer one or more tertiary doses “wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose,” in order to treat AMD.

120. Similarly, the YESAFILI™ label instructs physicians to treat the angiogenic eye disorders of DME and DR by administering 2 mg of YESAFILI™ (aflibercept-jbvf) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”¹¹² As I described above in connection with limitation (1a)—an analysis I incorporate herein by reference—this instruction directs physicians to administer one initial dose of 2 mg YESAFILI™ (aflibercept-jbvf), followed by a first “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks later, followed by a second “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks after that, followed by a third “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks after that, followed by a fourth “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks after that, followed by a “tertiary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) eight weeks after that (*i.e.*, eight weeks after the fourth , “secondary” dose), followed by additional “tertiary” doses of 2 mg YESAFILI™ (aflibercept-jbvf) at 8 week intervals thereafter. Thus, the YESAFILI™ label expressly recommends, encourages, and promotes physicians to administer one or more tertiary doses of YESAFILI™ (aflibercept-jbvf) “wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose,” in order to treat DME and in order to treat DR.¹¹³

¹¹² MYL-AFL-BLA1079688 at -1079688 to -1079689.

¹¹³ MYL-AFL-BLA1079688 at -1079688 to -1079689.

121. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform limitation (1c). In other words, if Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will administer YESAFILI™ such that each secondary dose is administered approximately 4 weeks following the immediately preceding dose.

122. Mylan's proposed labeling encourages, recommends, and promotes performance of limitation (1b) by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will administer YESAFILI™ such that each secondary dose is administered approximately 4 weeks following the immediately preceding dose in a manner consistent with Claim 1 of the '572 Patent, and specifically intends this infringing activity.

123. I also incorporate by reference my analysis of this limitation in the claim charts appended hereto as Appendix C as though set forth fully herein.

e) (1d) "wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose."

124. The POSA would understand Limitation (1d) to require that the physician who performed steps (1a) through (1c) of claim 1 also perform the step of measuring a gain in the visual acuity of the patient to whom the physician administered aflibercept no more than 52 weeks after administering the initial dose of aflibercept to that patient.

125. When treating patients for angiogenic eye disorders using Eylea®, physicians routinely perform the active step of measuring the visual acuity of their patients after a period of Eylea® administration. Physicians perform visual acuity measurements within 52 weeks of first administering Eylea® to a patient in order to assess whether the patient is experiencing the clinical benefits of Eylea®. For example, in one retrospective "real world" study of the use of intravitreal anti-VEGF agents (including aflibercept), data generated from routine clinical

practice was analyzed, and researchers found that one-year visual acuity data was available for more than half the patients for whom baseline data was available.¹¹⁴

126. Certainly, it is my own practice to actively measure the visual acuity of an AMD patient after I have administered an initial dose (at week 0), two secondary doses (at weeks 4 and 8), and one or more tertiary doses (beginning at week 16) of 2 mg Eylea®, and to do so before a year has passed since I administered the initial dose. Likewise, it is my practice to measure the visual acuity of a DME and/or DR patient after I have administered an initial dose (at week 0), four secondary doses (at weeks 4, 8, 12, and 16), and one or more tertiary doses (beginning at week 24) of 2 mg Eylea®, and to do so before 52 weeks have passed since I administered the initial dose. This is an active step I perform when I treat patients with Eylea®, and I view it as part of the treatment protocol for which I am responsible. I frequently discuss standards of care and clinical practice with other retinal specialists, and these conversations confirm my belief that other physicians share my practice—namely, that they actively measure the visual acuity of their patients after administering a tertiary dose of Eylea®, but before 52 weeks have passed.

127. Mylan's YESAFILI™ label instructs physicians that YESAFILI™ is interchangeable with Eylea®, and thereby instructs and encourages physicians to utilize YESAFILI™ in precisely the same way as physicians use Eylea®.¹¹⁵ By so doing, Mylan instructs and encourages physicians to perform the step of measuring their patients' visual acuity within 52 weeks of administering the initial dose of YESAFILI™, just as physicians would do

¹¹⁴ Arshad M. Khanani, M.D., M.A., *SIERRA-AMD: A Retrospective, Real-World Evidence Study of Patients with Neovascular Age-Related Macular Degeneration in the United States*, in Ophthalmology Retina Vol. 4 Issue 2, available at <https://www.sciencedirect.com/science/article/pii/S246865301930569X#tbl2> (2020) (Khanani 2020).

¹¹⁵ *Supra* Section VI.D.2.

for their use of Eylea®. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will measure their patients' visual acuity within 52 weeks of administering the initial dose of YESAFILI™.

128. Mylan's proposed labeling encourages, recommends, and promotes measuring patients' visual acuity within 52 weeks of administering the initial dose of YESAFILI™ by directing physicians to administer YESAFILI™ in the same way they administer Eylea®. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will administer YESAFILI™ to treat angiogenic eye disorders in a manner consistent with Claim 1 of the '572 Patent, and specifically intends this infringing activity.

129. I also incorporate by reference my analysis of this limitation in the claim charts appended hereto as Appendix C as though set forth fully herein.

1) Mylan Induces Physicians to Measure a Gain in Visual Acuity in Patients to Whom They Administer YESAFILI™ to Treat DME

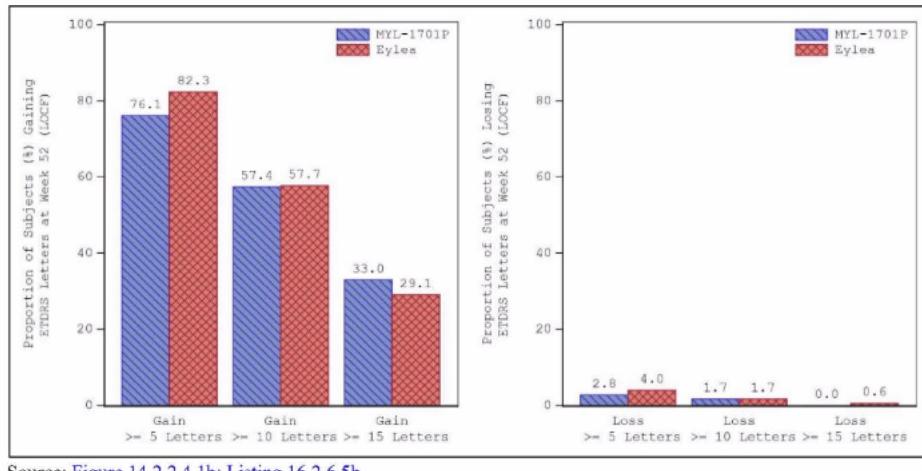
130. Mylan recommends, encourages, and promotes the use of YESAFILI™ to treat DME in a manner that practices limitations (1pre) through (1d) and recommends, encourages, and promotes physicians to measure a gain in visual acuity within 52 weeks of administering the initial dose of YESAFILI™.

i. Mylan's Phase III DME Study Results at 52 Weeks

131. Furthermore, when physicians perform the step of measuring their patients' visual acuity after having administered the first tertiary dose of YESAFILI™ within 52 weeks of administering the initial dose, as directed and encouraged by Mylan's proposed labeling, one or more physicians will measure a gain in visual acuity of their patient, consistent with limitation (1d). Indeed, when Mylan reported the results of its Phase III clinical trial in patients with DME to FDA, Mylan reported that as of 52 weeks, 76.1% of patients receiving YESAFILI™ on

Mylan's study regimen achieved a gain of 5 or more letters visual acuity, 57.4% of patients receiving YESAFILI™ on Mylan's study regimen achieved a gain of 10 or more letters visual acuity, and 33.0% of patients receiving YESAFILI™ on Mylan's study regimen achieved a gain of 15 or more letters visual acuity.¹¹⁶ These results are summarized by the graph below.¹¹⁷

Figure 11: Proportion of Subjects Who Gained or Lost ≥5, ≥10 or ≥15 Letters, at Week 52 (LOCF)



Source: Figure 14.2.2.4.1b; Listing 16.2.6.5b

132. Mylan's BLA states that 100 out of the 179 patients (55.9 %) who received YESAFILI™ as part of the DME clinical trial received nine doses of YESAFILI™, which means that physicians administered to those patients doses of 2mg YESAFILI™ at baseline and at weeks 4, 8, 12, 16, 24, 32, 40, and 48.¹¹⁸ Thus, in Mylan's DME study, a physician administered a treatment regimen consistent with limitations (1pre) through (1c) of claim 1 to at least 100 patients—*i.e.*, physicians administered one initial dose of 2 mg YESAFILI™ (at

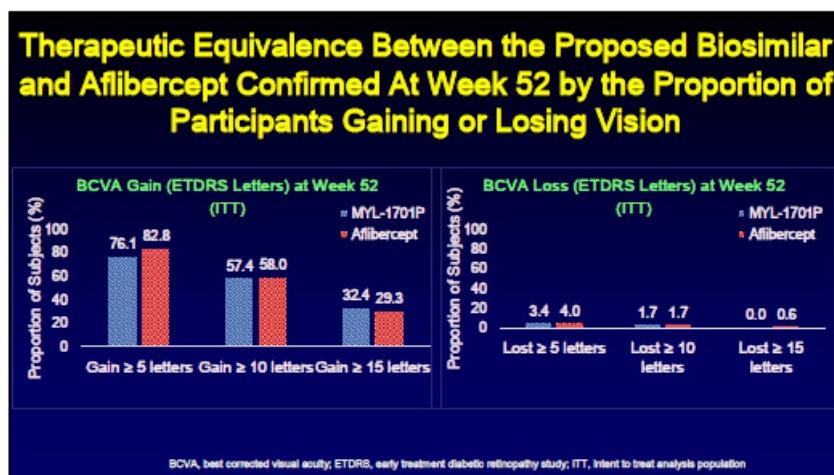
¹¹⁶ MYL-AFL-BLA1056844 at -1056950.

¹¹⁷ MYL-AFL-BLA1056844 at -1056950.

¹¹⁸ MYL-AFL-BLA1056844 at -1056950; MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486 (protocol defining dosing of YESAFILI™, and actions taken at each visit).

baseline), four secondary doses of 2 mg YESAFILI™ administered four weeks after the immediately preceding dose (at weeks 4, 8, 12, and 16), and four tertiary doses of 2 mg YESAFILI™ administered eight weeks after the immediately preceding dose (at weeks 24, 32, 40, and 48).¹¹⁹ Thus, patients who achieved a gain in visual acuity, as shown in the graph above, include patients who received a regimen of YESAFILI™ consistent with limitations (1pre) through (1c).

133. Mylan has also presented this information to doctors at conferences like AAO, where it touted the therapeutic equivalence of YESAFILI™ to Eylea®.¹²⁰



134. By presenting this information to doctors at conferences, and using it to promote YESAFILI™ as biosimilar to and/or interchangeable with Eylea®, Mylan recommends, encourages, and promotes the administration of YESAFILI™ in the same way as Eylea® and

¹¹⁹ MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486 (protocol defining dosing of YESAFILI™, and actions taken at each visit).

¹²⁰ MYL-AFL0089391 at -89399.

thus recommends, encourages and promotes the measurement of a gain in visual acuity within 52 weeks of the initial dose.

ii. Individual Patient Results in Mylan's Phase III Study.

135. Furthermore, Mylan submitted to FDA as part of its BLA visual acuity data for individual patients, measured at each study visit for its DME clinical trial.¹²¹ In combination with submissions that report which patients received doses of YESAFILI™ and when,¹²² this data demonstrates that physicians actually measured visual acuity gains in numerous patients who received one initial dose of 2 mg YESAFILI™ (aflibercept-jbvf), followed by four secondary doses of 2 mg YESAFILI™ (aflibercept-jbvf), administered four weeks after the immediately preceding dose, followed by one or more tertiary doses of 2 mg YESAFILI™ (aflibercept-jbvf).¹²³ Examples of such patients include patients with study numbers 110003, 110012, 117013, 202003, and 203007, among many others.¹²⁴

¹²¹ MYL-AFL-BLA1059735.

¹²² MYL-AFL-BLA1034645.

¹²³ Protocols for the week 52 (MYL-AFL-BLA1055435) clinical study report describes the treatment regimen patients receiving YESIFILI study patients could receive, and the criteria for administration of optional doses at, e.g., week 16. The drugs and dosing regimens actually administered to each patient are reported in MYL-AFL-BLA1034645.

¹²⁴ See MYL-AFL-BLA1034645 (Individual Batch Receipts); MYL-AFL-BLA1055435 (Protocols).

• Patient 110003

136. For example, Mylan's BLA shows that a physician administered doses of 2mg YESAFILI™ (aflibercept-jbvf) at baseline and at weeks, 4, 8, 12, 16, 24, 32, 40, and 48 to the patient with study number 110003 in Mylan's DME study.¹²⁵

Site: 110									
Subject Number	Age/Sex	Randomization Number	Treatment Group	Visit	Visit Number	Kit Number	Kit Status	Date the Kit was Dispensed	Label Lot Number of Kit
110001	62/M	102001	Eylea®	VISIT 15-WEEK 48	17	249576	RETURNED/DORDED STROYED	06AUG2019	P183731
110003	76/F	110004	MYL-1701P	VISIT 1-BASELINE	2	479516	RETURNED/DORDED STROYED	18SEP2018	P183731
				VISIT 4-WEEK 4	5	346517	RETURNED/DORDED STROYED	18OCT2018	P183731
				VISIT 5-WEEK 8	6	177269	RETURNED/DORDED STROYED	15NOV2018	P183731
				VISIT 6-WEEK 12	7	357047	RETURNED/DORDED STROYED	12DEC2018	P183731
				VISIT 7-WEEK 16	8	358403	RETURNED/DORDED STROYED	09JAN2019	P183731
				VISIT 9-WEEK 24	11	137236	RETURNED/DORDED STROYED	05MAR2019	P183731
				VISIT 11-WEEK 32	13	181111	RETURNED/DORDED STROYED	30APR2019	P183731
				VISIT 13-WEEK 40	15	228246	RETURNED/DORDED STROYED	25JUN2019	P183731
				VISIT 15-WEEK 48	17	327524	RETURNED/DORDED STROYED	20AUG2019	P183731

Note: Kit numbers that couldn't be assigned to subject due to a mismatch in the databases are described in the CSR.

Program Name: l_smlotb.SAS

DB Snapshot/Lock Date: 11Nov2021

Runtime: 29NOV2021 15:31

Confidential

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Thus, a physician administered to this patient a treatment regimen consistent with limitations (1pre) through (1c) of claim 1—*i.e.*, they administered one initial dose of 2 mg YESAFILI™ (aflibercept-jbvf) (at baseline), four secondary doses of 2 mg YESAFILI™ (aflibercept-jbvf) administered four weeks after the immediately preceding dose (at weeks 4, 8, 12, and 16), and

¹²⁵ MYL-AFL-BLA1034645 at -1034660 (batch receipts for patient 110003).

four tertiary doses of 2 mg YESAFILI™ (afibercept-jbv) administered eight weeks after the immediately preceding dose (at weeks 24, 32, 40, and 48).¹²⁶

137. Furthermore, Mylan's BLA shows that a physician performed step (1d) of claim 1 with respect to patient number 110003, because a physician measured a gain in visual acuity in patient number 110003 within 52 weeks following the initial dose.¹²⁷ I have highlighted the measurements the physician took at weeks 24 and 52 to for frame of reference.

Treatment Group: MYL-1701P				letter Score		Low Vision Testing					
Subject Number	Age/Sex	Visit	Date of Examination	Tester Initials	Eye	4 M	1 M	BCVA Score	Finger Counting	Hand Movements	Light Perception
109007	52/F	VISIT 15-WEEK 48	15OCT2020 09:56	TB	Study Eye	40	70				
				TB	Fellow Eye	36	66				
		VISIT 16-WEEK 52/EGT/EOS	16NOV2020 10:52	TB	Study Eye	35	65				
				TB	Fellow Eye	32	62				
110003	76/F	SCREENING	11SEP2018 09:10	ERM	Study Eye	28	58				
				ERM	Fellow Eye	35	65				
		VISIT 1-BASELINE	18SEP2018 12:14	ERM	Study Eye	28	58				
				ERM	Fellow Eye	27	57				
		VISIT 4-WEEK 4	18OCT2018 10:06	B G	Study Eye	38	68				
				B G	Fellow Eye	38	68				

FT = feet; M = meter; ND = Not done;

¹²⁶ MYL-AFL-BLA1034645 at -1034660 (batch receipts for patient 110003); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486 (protocol defining dosing of YESAFILI™, and actions taken at each visit).

¹²⁷ MYL-AFL-BLA1059735, at -1067687 to 106789 (showing BCVA scores at each visit for patient 110003).

Treatment Group: MYL-1701P

Subject Number	Age/ Sex	Visit	Date of Examination	Tester Initials	Eye	Letter Score		Low Vision Testing		
						4 M	1 M	BCVA Score	Finger Counting	Hand Movements
110003	76/F	VISIT 5-WEEK 8	15NOV2018 08:31	BG	Study Eye	39		69		
				BG	Fellow Eye	38		68		
		VISIT 6-WEEK 12	12DEC2018 08:15	BG	Study Eye	36		66		
				BG	Fellow Eye	39		69		
		VISIT 7-WEEK 16	09JAN2019 08:39	B G	Study Eye	38		68		
				B G	Fellow Eye	34		64		
		VISIT 8-WEEK 20	05FEB2019 12:53	BG	Study Eye	39		69		
				BG	Fellow Eye	40		70		
		VISIT 9-WEEK 24	05MAR2019 12:40	B G	Study Eye	43		73		
				B G	Fellow Eye	42		72		
		VISIT 10-WEEK 28	02APR2019 12:25	BG	Study Eye	42		72		
				BG	Fellow Eye	43		73		
		VISIT 11-WEEK 32	30APR2019 12:38	BG	Study Eye	44		74		

FT = feet; M = meter; ND = Not done;

Treatment Group: MYL-1701P

Subject Number	Age/ Sex	Visit	Date of Examination	Tester Initials	Eye	Letter Score		Low Vision Testing		
						4 M	1 M	BCVA Score	Finger Counting	Hand Movements
110003	76/F	VISIT 11-WEEK 32	30APR2019 12:38	BG	Fellow Eye	41		71		
		VISIT 12-WEEK 36	30MAY2019 08:15	BG	Study Eye	40		70		
				BG	Fellow Eye	44		74		
		VISIT 13-WEEK 40	25JUN2019 10:46	KS	Study Eye	44		74		
				KS	Fellow Eye	43		73		
		VISIT 14-WEEK 44	23JUL2019 10:42	KS	Study Eye	49		79		
				KS	Fellow Eye	44		74		
		VISIT 15-WEEK 48	20AUG2019 13:49	KS	Study Eye	44		74		
				KS	Fellow Eye	41		71		
		VISIT 16-WEEK 52/EOT/EOS	16SEP2019 08:25	KS	Study Eye	43		73		
				KS	Fellow Eye	37		67		

FT = feet; M = meter; ND = Not done;

138. Below, I have provided a table summarizing the gains a physician measured in patient 110003:

Week ¹²⁸	Visit Date ¹²⁹	2 mg of YESAFILITM administered? ¹³⁰	Gain Over Baseline According to ETDRS Letter Score ¹³¹
Baseline	September 18, 2018	Yes	0 (by definition)
Week 4	October 18, 2018	Yes	10
Week 8	November 15, 2018	Yes	11
Week 12	December 12, 2018	Yes	8
Week 16	January 9, 2018	Yes	10
Week 20	February 5, 2019	No	11
Week 24	March 5, 2019	Yes	15
Week 28	April 2, 2019	No	14
Week 32	April 20, 2019	Yes	16
Week 36	May 30, 2019	No	12
Week 40	June 25, 2018	Yes	16
Week 44	July 23, 2019	No	21
Week 48	August 20, 2019	Yes	16
Week 52	September 16, 2019	No	15

¹²⁸ MYL-AFL-BLA1059735, at -1067687 to -1067689 (showing BCVA scores at each visit for patient 110003 by week).

¹²⁹ MYL-AFL-BLA1059735, at -1067687 to -1067689 (reporting date of BCVA measurement); MYL-AFL-BLA1055435 at -1055481 to -1055486 (per protocol, BCVA measured on date of visit).

¹³⁰ MYL-AFL-BLA1034645 at -1034660 (batch receipts for patient 110003); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486 (protocol defining dosing of YESAFILITM, and actions taken at each visit).

¹³¹ MYL-AFL-BLA1059735, at -1067687 to -1067689 (showing BCVA scores at each visit for patient 110003).

139. Accordingly, a physician measured a gain in visual acuity within 52 weeks following the initial dose in patient No. 110003 in Mylan's DME study. By week 48 (*i.e.*, within 52 weeks), a physician measured a gain of 18 letters.¹³²

140. Other claims of the '572 patent place additional requirements on the measurement of visual acuity that the physician makes. The above BLA excerpts demonstrate that physicians made measurements meeting each of these requirements.

141. In particular, Claim 2 requires that the gain the physician measures is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score. As the BLA excerpts I cited above show, the measurements the physician performed on patient 110003 measured letter gains in visual acuity according to ETDRS letter score.¹³³

142. Claim 3 requires that a physician measure a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 52 weeks following the initial dose. The above chart demonstrates that at week 48 (*i.e.*, within 52 weeks), a physician measured a gain of 16 letters in patient 110003, which is a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹³⁴

¹³² MYL-AFL-BLA1059735, at -1067687 to 106789 (showing BCVA scores at each visit for patient 110003); MYL-AFL-BLA1034645 at -1034660 (batch receipts for patient 110003); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILI™, actions taken at each visit, and measurement of BCVA).

¹³³ MYL-AFL-BLA1059735, at -1067687 to 106789 (showing BCVA scores at each visit for patient 110003); MYL-AFL-BLA1034645 at -1034660 (batch receipts for patient 110003); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILI™, actions taken at each visit, and measurement of BCVA).

¹³⁴ MYL-AFL-BLA1059735, at -1067687 to 106789 (showing BCVA scores at each visit for patient 117012); MYL-AFL-BLA1034645 at -1034660 (batch receipts for patient 110003);

143. Claim 4 requires that a physician measure a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 24 weeks following the initial dose. The above chart demonstrates that at week 20 (*i.e.*, within 24 weeks), a physician measured a gain of 11 letters in patient 110003, which is a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹³⁵

144. Claims 8 and 21 require that a physician measure a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 52 weeks following the initial dose. The above chart demonstrates that at week 48 (*i.e.*, within 52 weeks), a physician measured a gain of 16 letters in patient 110003, which is a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹³⁶

145. Claim 9 requires that a physician measure a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 24 weeks following the initial dose. The above chart demonstrates that at week 20 (*i.e.*, within 24 weeks), a physician measured a gain of 11 letters in patient

MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

¹³⁵ MYL-AFL-BLA1059735, at -1067687 to 106789 (showing BCVA scores at each visit for patient 110003); MYL-AFL-BLA1034645 at -1034660 (batch receipts for patient 110003); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

¹³⁶ MYL-AFL-BLA1059735, at -1067687 to 106789 (showing BCVA scores at each visit for patient 110003); MYL-AFL-BLA1034645 at -1034660 (batch receipts for patient 110003); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

110003, which is a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹³⁷

146. Claims 10 and 17 require that a physician measure a gain of at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 52 weeks following the initial dose. The above chart demonstrates that at week 48 (*i.e.*, within 52 weeks), a physician measured a gain of 16 letters in patient 110003, which is a gain of at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹³⁸

147. Claim 20 requires that a physician measure a gain of at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 24 weeks following the initial dose (claim 20). The above chart demonstrates that at week 20 (*i.e.*, within 24 weeks), a physician measured a gain of 11 letters in patient 110003, which is a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹³⁹

¹³⁷ MYL-AFL-BLA1059735, at -1067687 to 106789 (showing BCVA scores at each visit for patient 117012); MYL-AFL-BLA1034645 at -1034660 (batch receipts for patient 110003); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILI™, actions taken at each visit, and measurement of BCVA).

¹³⁸ MYL-AFL-BLA1059735, at -1067687 to 106789 (showing BCVA scores at each visit for patient 110003); MYL-AFL-BLA1034645 at -1034660 (batch receipts for patient 110003); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILI™, actions taken at each visit, and measurement of BCVA).

¹³⁹ MYL-AFL-BLA1059735, at -1067687 to 106789 (showing BCVA scores at each visit for patient 110003); MYL-AFL-BLA1034645 at -1034660 (batch receipts for patient 110003); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILI™, actions taken at each visit, and measurement of BCVA).

• Patient 110012

148. By way of another example, Mylan's BLA shows that a physician administered doses of 2mg YESAFILI™ at baseline and at weeks 4, 8, 12, 16, 24, 32, 40, and 48 to the patient with study number 110012 in Mylan's DME study.¹⁴⁰

Site: 110

Subject Number	Age/Sex	Randomization Number	Treatment Group	Visit	Visit Number	Kit Number	Kit Status	Date the Kit was Dispensed	Label Lot Number of Kit
110011	61/F	102016	MYL-1701P	VISIT 5-WEEK 8	6	445795	RETURNEDORDE STROYED	19NOV2019	P183731
				VISIT 6-WEEK 12	7	203913	RETURNEDORDE STROYED	19DEC2019	P183731
				VISIT 7-WEEK 16	8	271487	RETURNEDORDE STROYED	14JAN2020	P183731
				VISIT 9-WEEK 24	11	388550	RETURNEDORDE STROYED	10MAR2020	P183731
				VISIT 11-WEEK 32	13	345476	RETURNEDORDE STROYED	05MAY2020	P183731
				VISIT 13-WEEK 40	15	119867	RETURNEDORDE STROYED	30JUN2020	P183731
				VISIT 15-WEEK 48	17	443021	RETURNEDORDE STROYED	25AUG2020	P183731
110012	63/M	102018	MYL-1701P	VISIT 1-BASELINE	2	115048	RETURNEDORDE STROYED	01OCT2019	P183731
				VISIT 4-WEEK 4	5	344229	RETURNEDORDE STROYED	29OCT2019	P183731
				VISIT 5-WEEK 8	6	422274	RETURNEDORDE STROYED	21NOV2019	P183731
				VISIT 6-WEEK 12	7	206301	RETURNEDORDE STROYED	17DEC2019	P183731

Site: 110

Subject Number	Age/Sex	Randomization Number	Treatment Group	Visit	Visit Number	Kit Number	Kit Status	Date the Kit was Dispensed	Label Lot Number of Kit
110012	63/M	102018	MYL-1701P	VISIT 7-WEEK 16	8	278983	RETURNEDORDE STROYED	14JAN2020	P183731
				VISIT 9-WEEK 24	11	275454	RETURNEDORDE STROYED	10MAR2020	P183731
				VISIT 11-WEEK 32	13	466172	RETURNEDORDE STROYED	08MAY2020	P183731
				VISIT 13-WEEK 40	15	365531	RETURNEDORDE STROYED	07JUL2020	P183731
				VISIT 15-WEEK 48	17	362304	RETURNEDORDE STROYED	01SEP2020	P183731

149. Thus, a physician administered to this patient a treatment regimen consistent with limitations (1pre) through (1c) of claim 1—*i.e.*, they administered one initial dose of 2 mg YESAFILI™ (afiblertcept-jbv) (at baseline), four secondary doses of 2 mg YESAFILI™ (afiblertcept-jbv) administered four weeks after the immediately preceding dose (at weeks 4, 8,

¹⁴⁰ MYL-AFL-BLA1034645 at -1034662 to -1034663 (batch receipts for patient 110012).

12, and 16), and four tertiary doses of 2 mg YESAFILI™ (afibercept-jbvf) administered eight weeks after the immediately preceding dose (at weeks 24, 32, 40, and 48).¹⁴¹

150. Furthermore, Mylan's BLA shows that a physician performed step (1d) of claim 1 with respect to patient number 110012, because physicians measured a gain in visual acuity in patient number 110012 within 52 weeks following the initial dose.¹⁴² I have highlighted the measurements the physician took at weeks 24 and 52 to for frame of reference.

Treatment Group: MYL-1701P				Letter Score		Low Vision Testing					
Subject Number	Age/ Sex	Visit	Date of Examination	Tester Initials	Eye	4 M	1 M	BCVA Score	Finger Counting	Hand Movements	Light Perception
110011	61/F	VISIT 14-WEEK 44	04AUG2020 08:45	KS	Study Eye	40	70				
				KS	Fellow Eye	50	80				
		VISIT 15-WEEK 48	25AUG2020 13:33	KS	Study Eye	37	67				
				KS	Fellow Eye	37	67				
		VISIT 16-WEEK 52/BOT/EOS	24SEP2020 15:00	KS	Study Eye	41	71				
				KS	Fellow Eye	43	73				
110012	63/M	SCREENING	23SEP2019 11:17	KS	Study Eye	40	70				
				KS	Fellow Eye	55	85				
		VISIT 1-BASELINE	01OCT2019 13:46	KS	Study Eye	38	68				
				KS	Fellow Eye	53	83				
		VISIT 4-WEEK 4	29OCT2019 13:20	K-S	Study Eye	53	83				

FT = feet; M = meter; ND = Not done;

¹⁴¹ MYL-AFL-BLA1034645 at -1034662 to -1034663 (batch receipts for patient 110012); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486 (protocol defining dosing of YESAFILI™, and actions taken at each visit).

¹⁴² MYL-AFL-BLA1059735, at -1067692 to -1067694 (showing BCVA scores at each visit for patient 110012).

Treatment Group: MYL-1701P

Subject Number	Age/ Sex	Visit	Date of Examination	Tester Initials	Eye	Letter Score			Low Vision Testing		
						4 M	1 M	BCVA Score	Finger Counting	Hand Movements	Light Perception
110012	63/M	VISIT 4-WEEK 4	29OCT2019 13:20	K-S	Fellow Eye	53		83			
		VISIT 5-WEEK 8	21NOV2019 09:15	K-S	Study Eye	52		82			
				K-S	Fellow Eye	54		84			
		VISIT 6-WEEK 12	17DEC2019 10:42	K-S	Study Eye	52		82			
				K-S	Fellow Eye	50		80			
		VISIT 7-WEEK 16	14JAN2020 11:05	K-S	Study Eye	54		84			
				K-S	Fellow Eye	55		85			
		VISIT 8-WEEK 20	11FEB2020 10:15	K-S	Study Eye	54		84			
				K-S	Fellow Eye	59		89			
		VISIT 9-WEEK 24	10MAR2020 10:35	K-S	Study Eye	55		85			
				K-S	Fellow Eye	58		88			
		VISIT 10-WEEK 28	07APR2020 11:55	K-S	Study Eye	59		89			
				K-S	Fellow Eye	54		84			

FT = feet; M = meter; ND = Not done;

Treatment Group: MYL-1701P

Subject Number	Age/ Sex	Visit	Date of Examination	Tester Initials	Eye	Letter Score			Low Vision Testing		
						4 M	1 M	BCVA Score	Finger Counting	Hand Movements	Light Perception
110012	63/M	VISIT 11-WEEK 32	08MAY2020 12:15	KS	Study Eye	57		87			
				KS	Fellow Eye	48		78			
		VISIT 12-WEEK 36	09JUN2020 11:17	KS	Study Eye	52		82			
				KS	Fellow Eye	54		84			
		VISIT 13-WEEK 40	07JUL2020 13:40	KS	Study Eye	57		87			
				KS	Fellow Eye	58		88			
		VISIT 14-WEEK 44	11AUG2020 14:28	KS	Study Eye	55		85			
				KS	Fellow Eye	54		84			
		VISIT 15-WEEK 48	01SEP2020 14:25	KS	Study Eye	56		86			
				KS	Fellow Eye	54		84			
		VISIT 16-WEEK 52/EOT/EOS	28SEP2020 13:45	KS	Study Eye	56		86			

FT = feet; M = meter; ND = Not done;

151. Below, I have provided a table summarizing the gains a physician measured in patient 110012:

Week ¹⁴³	Visit Date ¹⁴⁴	2 mg of YESAFILI™ administered? ¹⁴⁵	Gain Over Baseline According to ETDRS Letter Score ¹⁴⁶
Baseline	October 1, 2019	Yes	0 (by definition)
Week 4	October 29, 2019	Yes	15
Week 8	November 21, 2019	Yes	14
Week 12	December 17, 2019	Yes	14
Week 16	January 14, 2020	Yes	16
Week 20	February 11, 2020	No	16
Week 24	March 10, 2020	Yes	17
Week 28	April 7, 2020	No	21
Week 32	May 8, 2020	Yes	19
Week 36	June 9, 2020	No	14
Week 40	July 7, 2020	Yes	19
Week 44	August 11, 2020	No	17
Week 48	September 1, 2020	Yes	18
Week 52	September 28, 2020	No	18

¹⁴³ MYL-AFL-BLA1059735, at -1067692 to -1067694 (showing BCVA scores at each visit for patient 110012); MYL-AFL-BLA1034645 at -1034662 to -1034663 (batch receipts for patient 110012).

¹⁴⁴ MYL-AFL-BLA1059735, at -1067692 to -1067694 (date of visit is same as date of study administration, per protocol); MYL-AFL-BLA1055435 at -1055481 to -1055486 (protocol per visit).

¹⁴⁵ MYL-AFL-BLA1034645 at -1034662 to -1034663 (batch receipts for patient 110012); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486 (protocol defining dosing of YESAFILI™, and actions taken at each visit).

¹⁴⁶ MYL-AFL-BLA1059735, at -1067692 to -1067694 (showing BCVA scores at each visit for patient 110012).

152. Accordingly, a physician measured a gain in visual acuity within 52 weeks following the initial dose in patient No. 1171012 in Mylan's DME study. By week 48 (*i.e.*, within 52 weeks), a physician measured a gain of 18 letters.

153. Other claims of the '572 patent place additional requirements on the measurement of visual acuity that the physician makes. The above BLA excerpts demonstrate that physicians made measurements meeting each of these requirements.

154. In particular, Claim 2 requires that the gain the physician measures is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score. As the BLA excerpts I cited above show, the measurements the physician performed on patient 1171012 measured letter gains in visual acuity according to ETDRS letter score.¹⁴⁷

155. Claim 3 requires that a physician measure a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 52 weeks following the initial dose. The above chart demonstrates that at week 48 (*i.e.*, within 52 weeks), physicians measured a gain of 18 letters in patient 1171012, which is a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁴⁸

¹⁴⁷ MYL-AFL-BLA1059735, at -1067692 to -1067694 (showing BCVA scores at each visit for patient 117012); MYL-AFL-BLA1034645 at -1034662 to -1034663 (batch receipts for patient 117012); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

¹⁴⁸ MYL-AFL-BLA1059735, at -1067692 to -1067694 (showing BCVA scores at each visit for patient 117012); MYL-AFL-BLA1034645 at -1034662 to -1034663 (batch receipts for patient 117012); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

156. Claim 4 requires that a physician measure a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 24 weeks following the initial dose. The above chart demonstrates that at week 20 (*i.e.*, within 24 weeks), physicians measured a gain of 16 letters in patient 1171012, which is a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁴⁹

157. Claims 8 and 21 require that a physician measure a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 52 weeks following the initial dose. The above chart demonstrates that at week 48 (*i.e.*, within 52 weeks), physicians measured a gain of 18 letters in patient 1171012, which is a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁵⁰

158. Claim 9 requires that a physician measure a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 24 weeks following the initial dose. The above chart demonstrates that at week 20 (*i.e.*, within 24 weeks), physicians measured a gain of 16 letters in patient

¹⁴⁹ MYL-AFL-BLA1059735, at -1067692 to -1067694 (showing BCVA scores at each visit for patient 117012); MYL-AFL-BLA1034645 at -1034662 to -1034663 (batch receipts for patient 117012); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

¹⁵⁰ MYL-AFL-BLA1059735, at -1067692 to -1067694 (showing BCVA scores at each visit for patient 117012); MYL-AFL-BLA1034645 at -1034662 to -1034663 (batch receipts for patient 117012); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

1171013, which is a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁵¹

159. Claims 10 and 17 require that a physician measure a gain of at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 52 weeks following the initial dose. The above chart demonstrates that at week 48 (*i.e.*, within 52 weeks), physicians measured a gain of 18 letters in patient 1171013, which is a gain of at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁵²

160. Claim 20 requires that a physician measure a gain of at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 24 weeks following the initial dose (claim 20). The above chart demonstrates that at week 20 (*i.e.*, within 24 weeks), physicians measured a gain of 16 letters in patient 1171013, which is a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁵³

¹⁵¹ MYL-AFL-BLA1059735, at -1067692 to -1067694 (showing BCVA scores at each visit for patient 117012); MYL-AFL-BLA1034645 at -1034662 to -1034663 (batch receipts for patient 117012); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

¹⁵² MYL-AFL-BLA1059735, at -1067692 to -1067694 (showing BCVA scores at each visit for patient 117012); MYL-AFL-BLA1034645 at -1034662 to -1034663 (batch receipts for patient 117012); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

¹⁵³ MYL-AFL-BLA1059735, at -1067692 to -1067694 (showing BCVA scores at each visit for patient 117012); MYL-AFL-BLA1034645 at -1034662 to -1034663 (batch receipts for patient 117012); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

• Patient 117013

161. By way of another example, Mylan's BLA shows that a physician administered doses of 2mg YESAFILI™ at baseline and at weeks 4, 8, 12, 16, 24, 32, 40, and 48 to the patient with study number 117013 in Mylan's DME study.¹⁵⁴

Site: 117									
Subject Number	Age/Sex	Randomization Number	Treatment Group	Visit	Visit Number	Kit Number	Kit Status	Date the Kit was Dispensed	Label Lot Number of Kit
117012	69/M	110015	MYL-1701P	VISIT 1-BASELINE	2	450306	RETURNEDORDE STROYED	29MAY2019	P183731
				VISIT 4-WEEK 4	5	448727	RETURNEDORDE STROYED	25JUN2019	P183731
				VISIT 5-WEEK 8	6	230912	RETURNEDORDE STROYED	30JUL2019	P183731
				VISIT 6-WEEK 12	7	269541	RETURNEDORDE STROYED	27AUG2019	P183731
				VISIT 7-WEEK 16	8	465619	RETURNEDORDE STROYED	23SEP2019	P183731
				VISIT 9-WEEK 24	11	221084	RETURNEDORDE STROYED	14NOV2019	P183731
				VISIT 11-WEEK 32	13	173593	RETURNEDORDE STROYED	15JAN2020	P183731
				VISIT 13-WEEK 40	15	393553	RETURNEDORDE STROYED	04MAR2020	P183731
				VISIT 15-WEEK 48	17	398404	RETURNEDORDE STROYED	04MAY2020	P183731
117013	69/M	110016	MYL-1701P	VISIT 1-BASELINE	2	183193	RETURNEDORDE STROYED	09JUL2019	P183731
				VISIT 4-WEEK 4	5	334600	RETURNEDORDE STROYED	13AUG2019	P183731

Note: Kit numbers that couldn't be assigned to subject due to a mismatch in the databases are described in the CSR.

Site: 117									
Subject Number	Age/Sex	Randomization Number	Treatment Group	Visit	Visit Number	Kit Number	Kit Status	Date the Kit was Dispensed	Label Lot Number of Kit
117013	69/M	110016	MYL-1701P	VISIT 5-WEEK 8	6	433591	RETURNEDORDE STROYED	09SEP2019	P183731
				VISIT 6-WEEK 12	7	466435	RETURNEDORDE STROYED	04OCT2019	P183731
				VISIT 7-WEEK 16	8	412032	RETURNEDORDE STROYED	29OCT2019	P183731
				VISIT 9-WEEK 24	11	274987	RETURNEDORDE STROYED	31DEC2019	P183731
				VISIT 11-WEEK 32	13	207434	RETURNEDORDE STROYED	25FEB2020	P183731
				VISIT 13-WEEK 40	15	322888	RETURNEDORDE STROYED	20APR2020	P183731
				VISIT 15-WEEK 48	17	230667	RETURNEDORDE STROYED	11JUN2020	P183731

162. Thus, a physician administered to this patient a treatment regimen consistent with limitations (1pre) through (1c) of claim 1—*i.e.*, they administered one initial dose of 2 mg YESAFILI™ (afiblertcept-jbv) (at baseline), four secondary doses of 2 mg YESAFILI™

¹⁵⁴ MYL-AFL-BLA1034645 at -1034685 (batch receipts for patient 117013).

(aflibercept-jbvf) administered four weeks after the immediately preceding dose (at weeks 4, 8, 12, and 16), and four tertiary doses of 2 mg YESAFILI™ (aflibercept-jbvf) administered eight weeks after the immediately preceding dose (at weeks 24, 32, 40, and 48).¹⁵⁵

163. Furthermore, Mylan's BLA shows that a physician performed step (1d) of claim 1 with respect to patient number 117013, because physicians measured a gain in visual acuity in patient number 117013 within 52 weeks following the initial dose.¹⁵⁶ I have highlighted the measurements the physician took at weeks 24 and 52 for reference.

Listing 16.2.6.5b Best-Corrected Visual Acuity Safety Analysis Set													
Treatment Group: MYL-1701P													
Subject Number	Age/ Sex	Visit	Date of Examination	Tester Initials	Eye	Letter Score		Low Vision Testing					
						4 M	1 M	BCVA Score	Finger Counting	Hand Movements	Light Perception		
117012	69/M	VISIT 16-WEEK 52/EOT/EOS	26MAY2020 10:12	PF	Study Eye	48		78					
				PF	Fellow Eye	56		86					
117013	69/M	SCREENING	20JUN2019 09:24	LH	Study Eye	43		73					
					Fellow Eye	38		68					
VISIT 1-BASELINE			09JUL2019 12:52	LH	Study Eye	43		73					
				LH	Fellow Eye	34		64					
VISIT 4-WEEK 4			13AUG2019 08:57	PF	Study Eye	50		80					
				PF	Fellow Eye	29		59					
VISIT 5-WEEK 8			09SEP2019 08:36	AR	Study Eye	47		77					
				AR	Fellow Eye	37		67					
VISIT 6-WEEK 12			04OCT2019 09:00	AR	Study Eye	50		80					

FT = feet; M = meter; ND = Not done;

¹⁵⁵ MYL-AFL-BLA1034645 at -1034685 (batch receipts for patient 117013); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486 (protocol defining dosing of YESAFILI™, and actions taken at each visit).

¹⁵⁶ MYL-AFL-BLA1059735, at -1067725 to -1067727 (showing BCVA scores at each visit for patient 117013).

Treatment Group: MYL-1701P

Subject Number	Age/ Sex	Visit	Date of Examination	Tester Initials	Eye	Letter Score			Low Vision Testing		
						4 M	1 M	BCVA Score	Finger Counting	Hand Movements	Light Perception
117013	69/M	VISIT 6-WEEK 12	04OCT2019 09:00	AR	Fellow Eye	44		74			
		VISIT 7-WEEK 16	29OCT2019 08:45		Study Eye	50		80			
				AR	Fellow Eye	40		70			
		VISIT 8-WEEK 20	05DEC2019 08:37		Study Eye	55		85			
				AR	Fellow Eye	40		70			
		VISIT 9-WEEK 24	31DEC2019 10:47		Study Eye	54		84			
					Fellow Eye	44		74			
		VISIT 10-WEEK 28	21JAN2020 10:05	MR	Study Eye	54		84			
					Fellow Eye	43		73			
		VISIT 11-WEEK 32	25FEB2020 13:21	AR	Study Eye	53		83			
					Fellow Eye	43		73			
		VISIT 12-WEEK 36	24MAR2020 08:55	MR	Study Eye	55		85			
					Fellow Eye	44		74			

FT = feet; M = meter; ND = Not done;

Treatment Group: MYL-1701P

Subject Number	Age/ Sex	Visit	Date of Examination	Tester Initials	Eye	Letter Score			Low Vision Testing		
						4 M	1 M	BCVA Score	Finger Counting	Hand Movements	Light Perception
117013	69/M	VISIT 13-WEEK 40	20APR2020 09:20	PF	Study Eye	53		83			
					Fellow Eye	40		70			
		VISIT 14-WEEK 44	14MAY2020 08:49	PF	Study Eye	54		84			
					Fellow Eye	39		69			
		VISIT 15-WEEK 48	11JUN2020 09:30	MH	Study Eye	54		84			
					Fellow Eye	40		70			
		VISIT 16-WEEK 52/BOT/EOS	14JUL2020 08:56	MH	Study Eye	55		85			
					Fellow Eye	40		70			

164. Below, I have provided a table summarizing the gains a physician measured in patient 117013:

Week ¹⁵⁷	Visit Date ¹⁵⁸	2 mg of YESAFILI™ administered? ¹⁵⁹	Gain Over Baseline According to ETDRS Letter Score ¹⁶⁰
Baseline	July 9, 2019	Yes	0 (by definition)
Week 4	August 13, 2019	Yes	7
Week 8	September 9, 2019	Yes	4
Week 12	October 4, 2019	Yes	7
Week 16	October 29, 2019	Yes	7
Week 20	December 5, 2019	No	12
Week 24	December 31, 2019	Yes	11
Week 28	January 21, 2020	No	11
Week 32	February 25, 2020	Yes	10
Week 36	March 24, 2020	No	12
Week 40	April 20, 2020	Yes	10
Week 44	May 14, 2020	No	11
Week 48	Jun 11, 2020	Yes	11
Week 52	July 14, 2020	No	12

¹⁵⁷ MYL-AFL-BLA1059735, at -1067725 to -1067727 (showing BCVA scores at each visit for patient 117013); MYL-AFL-BLA1034645 at -1034685 (batch receipts for patient 117013).

¹⁵⁸ MYL-AFL-BLA1059735, at -1067725 to -1067727 (date of visit is same as date of study administration, per protocol); MYL-AFL-BLA1055435 at -1055481 to -1055486 (protocol per visit).

¹⁵⁹ MYL-AFL-BLA1034645 at -1034662 to -1034663 (batch receipts for patient 117013); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486 (protocol defining dosing of YESAFILI™, and actions taken at each visit).

¹⁶⁰ MYL-AFL-BLA1059735, at -1067725 to -1067727 (showing BCVA scores at each visit for patient 117013).

165. Accordingly, a physician measured a gain in visual acuity within 52 weeks following the initial dose in patient No. 117013 in Mylan's DME study. By week 48 (*i.e.*, within 52 weeks), a physician measured a gain of 11 letters.

166. Other claims of the '572 patent place additional requirements on the measurement of visual acuity that the physician makes. The above BLA excerpts demonstrate that physicians made measurements meeting each of these requirements.¹⁶¹

167. In particular, Claim 2 requires that the gain the physician measures is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score. As the BLA excerpts I cited above show, the measurements the physician performed on patient 117013 reported letter gains in visual acuity according to ETDRS letter score.¹⁶²

168. Claim 3 requires that a physician measure a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 52 weeks following the initial dose. The above chart demonstrates that at week 48 (*i.e.*, within 52 weeks), physicians measured a gain of 11 letters in patient 117013, which is a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁶³

¹⁶¹ MYL-AFL-BLA1059735, at -1067725 to -1067727 (showing BCVA scores at each visit for patient 117013); MYL-AFL-BLA1034645 at -1034685 (batch receipts for patient 117013); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILI™, actions taken at each visit, and measurement of BCVA).

¹⁶² MYL-AFL-BLA1059735, at -1067725 to -1067727 (showing BCVA scores at each visit for patient 117013); MYL-AFL-BLA1034645 at -1034685 (batch receipts for patient 117013); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILI™, actions taken at each visit, and measurement of BCVA).

¹⁶³ MYL-AFL-BLA1059735, at -1067725 to -1067727 (showing BCVA scores at each visit for patient 117013); MYL-AFL-BLA1034645 at -1034685 (batch receipts for patient 117013);

169. Claim 4 requires that a physician measure a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 24 weeks following the initial dose. The above chart demonstrates that at week 20 (*i.e.*, within 24 weeks), physicians measured a gain of 12 letters in patient 117013, which is a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁶⁴

170. Claims 8 and 21 require that a physician measure a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 52 weeks following the initial dose. The above chart demonstrates that at week 48 (*i.e.*, within 52 weeks), physicians measured a gain of 11 letters in patient 117013, which is a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁶⁵

171. Claim 9 requires that a physician measure a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 24 weeks following the initial dose. The above chart demonstrates that at week 20 (*i.e.*, within 24 weeks), physicians measured a gain of 12 letters in patient

MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

¹⁶⁴ MYL-AFL-BLA1059735, at -1067725 to -1067727 (showing BCVA scores at each visit for patient 117013); MYL-AFL-BLA1034645 at -1034685 (batch receipts for patient 117013); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

¹⁶⁵ MYL-AFL-BLA1059735, at -1067725 to -1067727 (showing BCVA scores at each visit for patient 117013); MYL-AFL-BLA1034645 at -1034685 (batch receipts for patient 117013); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

117013, which is a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁶⁶

172. Claims 10 and 17 require that a physician measure a gain of at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 52 weeks following the initial dose. The above chart demonstrates that at week 48 (*i.e.*, within 52 weeks), physicians measured a gain of 11 letters in patient 117013, which is a gain of at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁶⁷

173. Claim 20 requires that a physician measure a gain of at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 24 weeks following the initial dose (claim 20). The above chart demonstrates that at week 20 (*i.e.*, within 24 weeks), physicians measured a gain of 12 letters in patient 117013, which is a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁶⁸

¹⁶⁶ MYL-AFL-BLA1059735, at -1067725 to -1067727 (showing BCVA scores at each visit for patient 117013); MYL-AFL-BLA1034645 at -1034685 (batch receipts for patient 117013); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

¹⁶⁷ MYL-AFL-BLA1059735, at -1067725 to -1067727 (showing BCVA scores at each visit for patient 117013); MYL-AFL-BLA1034645 at -1034685 (batch receipts for patient 117013); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

¹⁶⁸ MYL-AFL-BLA1059735, at -1067725 to -1067727 (showing BCVA scores at each visit for patient 117013); MYL-AFL-BLA1034645 at -1034685 (batch receipts for patient 117013); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

• Patient 202003

174. By way of another example, Mylan's BLA shows that a physician administered doses of 2mg YESAFILI™ at baseline and at weeks 4, 8, 12, 16, 24, 32, 40, and 48 to the patient with study number 202003 in Mylan's DME study.¹⁶⁹

Site: 202									
Subject Number	Age/ Sex	Randomization Number	Treatment Group	Visit	Visit Number	Kit Number	Kit Status	Date the Kit was Dispensed	Label Lot Number of Kit
202003	68/M	112033	MYL-1701P	VISIT 1-BASELINE	2	242998	RETURNEDORDE STROYED	20MAY2019	P183731
				VISIT 4-WEEK 4	5	191430	RETURNEDORDE STROYED	17JUN2019	P183731
				VISIT 5-WEEK 8	6	423121	RETURNEDORDE STROYED	17JUL2019	P183731
				VISIT 6-WEEK 12	7	180060	RETURNEDORDE STROYED	13AUG2019	P183731
				VISIT 7-WEEK 16	8	252904	RETURNEDORDE STROYED	13SEP2019	P183731
				VISIT 9-WEEK 24	11	303858	RETURNEDORDE STROYED	01NOV2019	P183731
				VISIT 11-WEEK 32	13	348235	RETURNEDORDE STROYED	23DEC2019	P183731
				VISIT 13-WEEK 40	15	340751	RETURNEDORDE STROYED	21FEB2020	P183731
				VISIT 15-WEEK 48	17	339426	RETURNEDORDE STROYED	24APR2020	P183731

175. Thus, a physician administered to this patient a treatment regimen consistent with limitations (1pre) through (1c) of claim 1—*i.e.*, they administered one initial dose of 2 mg YESAFILI™ (aflibercept-jbv) (at baseline), four secondary doses of 2 mg YESAFILI™ (aflibercept-jbv) administered four weeks after the immediately preceding dose (at weeks 4, 8, 12, and 16), and four tertiary doses of 2 mg YESAFILI™ (aflibercept-jbv) administered eight weeks after the immediately preceding dose (at weeks 24, 32, 40, and 48).¹⁷⁰

176. Furthermore, Mylan's BLA shows that a physician performed step (1d) of claim 1 with respect to patient number 202003, because physicians measured a gain in visual acuity in

¹⁶⁹ MYL-AFL-BLA1034645 at -1034705 (batch receipts for patient 202003).

¹⁷⁰ MYL-AFL-BLA1034645 at -1034705 (batch receipts for patient 202003); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486 (protocol defining dosing of YESAFILI™, and actions taken at each visit).

patient number 202003 within 52 weeks following the initial dose.¹⁷¹ I have highlighted the measurements the physician took at weeks 24 and 52 for reference.

Treatment Group: MYL-1701P

Subject Number	Age/ Sex	Visit	Date of Examination	Tester Initials	Eye	Letter Score		Low Vision Testing		
						4 M	1 M	BCVA Score	Finger Counting	Hand Movements
128005	67/F	VISIT 15-WEEK 48	15JUL2020 09:05	AJ	Study Eye	25		55		
				AJ	Fellow Eye	20		50		
	VISIT 16-WEEK 52/BOT/EOS	19AUG2020 09:20	AJ	Study Eye	27		57			
			AJ	Fellow Eye	39		69			
	202003	68/M SCREENING	24APR2019 12:23	SK	Study Eye	38		68		
VISIT 1-BASELINE 20MAY2019 08:37					SK	Study Eye	37	67		
					SK	Fellow Eye	52	82		
VISIT 4-WEEK 4					SK	Study Eye	43	73		
					SK	Fellow Eye	55	85		

FT = feet; M = meter; ND = Not done;

Treatment Group: MYL-1701P

Subject Number	Age/ Sex	Visit	Date of Examination	Tester Initials	Eye	Letter Score		Low Vision Testing			
						4 M	1 M	BCVA Score	Finger Counting	Hand Movements	
202003	68/M	VISIT 5-WEEK 8	17JUL2019 10:40	SK	Study Eye	39		69			
				SK	Fellow Eye	54		84			
	VISIT 6-WEEK 12	13AUG2019 10:28	SK	Study Eye	48		78				
			SK	Fellow Eye	55		85				
	VISIT 7-WEEK 16	13SEP2019 10:00	SK	Study Eye	48		78				
			SK	Fellow Eye	55		85				
VISIT 8-WEEK 20 04OCT2019 10:15					SK	Study Eye	49	79			
					SK	Fellow Eye	55	85			
VISIT 9-WEEK 24 01NOV2019 11:39					SK	Study Eye	49	79			
					SK	Fellow Eye	55	85			
VISIT 10-WEEK 28 06DEC2019 08:00					PH	Study Eye	51	81			
					PH	Fellow Eye	55	85			
VISIT 11-WEEK 32 23DEC2019 08:40					PH	Study Eye	50	80			

FT = feet; M = meter; ND = Not done;

¹⁷¹ MYL-AFL-BLA1059735, at -1067757 to -1067759 (showing BCVA scores at each visit for patient 202003).

Listing 16.2.6.5b Best-Corrected Visual Acuity
Safety Analysis Set

Treatment Group: MYL-1701P

Subject Number	Age/ Sex	Visit	Date of Examination	Tester Initials	Eye	Letter Score		Low Vision Testing			
						4 M	1 M	BCVA Score	Finger Counting	Hand Movements	Light Perception
202003	68/M	VISIT 11-WEEK 32	23DEC2019 08:40	PH	Fellow Eye	57		87			
		VISIT 12-WEEK 36	24JAN2020 10:40	PH	Study Eye	51		81			
				PH	Fellow Eye	55		85			
		VISIT 13-WEEK 40	21FEB2020 10:42	PH	Study Eye	49		79			
				PH	Fellow Eye	55		85			
		VISIT 14-WEEK 44	25MAR2020 09:33	SK	Study Eye	49		79			
				SK	Fellow Eye	55		85			
		VISIT 15-WEEK 48	24APR2020 09:40	SK	Study Eye	51		81			
				SK	Fellow Eye	57		87			
		VISIT 16-WEEK 52/BOT/EOS	25MAY2020 09:47	SK	Study Eye	50		80			
				SK	Fellow Eye	56		86			

FT = feet; M = meter; ND = Not done;

177. Below, I have provided a table summarizing the gains a physician measured in patient 202003:

Week ¹⁷²	Visit Date ¹⁷³	2 mg of YESAFILI™ administered? ¹⁷⁴	Gain Over Baseline According to ETDRS Letter Score ¹⁷⁵
Baseline	May 20, 2019	Yes	0 (by definition)
Week 4	June 17, 2019	Yes	6
Week 8	July 17, 2019	Yes	2
Week 12	August 13, 2019	Yes	11

¹⁷² MYL-AFL-BLA1059735, at -1067757 to -1067759 (showing BCVA scores at each visit for patient 202003); MYL-AFL-BLA1034645 at -1034705 (batch receipts for patient 202003).

¹⁷³ MYL-AFL-BLA1059735, at -1067757 to -1067759 (date of visit is same as date of study administration, per protocol); MYL-AFL-BLA1055435 at -1055481 to -1055486 (protocol per visit).

¹⁷⁴ MYL-AFL-BLA1034645 at -1034705 (batch receipts for patient 202003); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486 (protocol defining dosing of YESAFILI™, and actions taken at each visit).

¹⁷⁵ MYL-AFL-BLA1059735, at -1067757 to -1067759 (showing BCVA scores at each visit for patient 202003).

Week 16	September 13, 2019	Yes	11
Week 20	October 4, 2019	No	12
Week 24	November 1, 2019	Yes	12
Week 28	December 6, 2019	No	14
Week 32	December 23, 2019	Yes	13
Week 36	January 24, 2020	No	14
Week 40	February 21, 2020	Yes	12
Week 44	March 25, 2020	No	12
Week 48	April 24, 2020	Yes	14
Week 52	May 25, 2020	No	13

178. Accordingly, a physician measured a gain in visual acuity within 52 weeks following the initial dose in patient No. 202003 in Mylan's DME study. By week 48 (*i.e.*, within 52 weeks), a physician measured a gain of 14 letters.

179. Other claims of the '572 patent place additional requirements on the measurement of visual acuity that the physician makes. The above BLA excerpts demonstrate that physicians made measurements meeting each of these requirements.¹⁷⁶

180. In particular, Claim 2 requires that the gain the physician measures is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score. As the BLA excerpts I cited

¹⁷⁶ MYL-AFL-BLA1059735, at -1067757 to -1067759 (showing BCVA scores at each visit for patient 202003); MYL-AFL-BLA1034645 at -1034705 (batch receipts for patient 202003); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, -1055488 (protocol defining dosing of YESAFILI™, actions taken at each visit, and measurement of BCVA).

above show, the measurements the physician performed on patient 202003 reported letter gains in visual acuity according to ETDRS letter score.¹⁷⁷

181. Claim 3 requires that a physician measure a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 52 weeks following the initial dose. The above chart demonstrates that at week 48 (*i.e.*, within 52 weeks), physicians measured a gain of 14 letters in patient 202003, which is a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁷⁸

182. Claim 4 requires that a physician measure a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 24 weeks following the initial dose. The above chart demonstrates that at week 20 (*i.e.*, within 24 weeks), physicians measured a gain of 12 letters in patient 202003, which is a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁷⁹

¹⁷⁷ MYL-AFL-BLA1059735, at -1067757 to -1067759 (showing BCVA scores at each visit for patient 202003); MYL-AFL-BLA1034645 at -1034705 (batch receipts for patient 202003); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILI™, actions taken at each visit, and measurement of BCVA).

¹⁷⁸ MYL-AFL-BLA1059735, at -1067757 to -1067759 (showing BCVA scores at each visit for patient 202003); MYL-AFL-BLA1034645 at -1034705 (batch receipts for patient 202003); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILI™, actions taken at each visit, and measurement of BCVA).

¹⁷⁹ MYL-AFL-BLA1059735, at -1067757 to -1067759 (showing BCVA scores at each visit for patient 202003); MYL-AFL-BLA1034645 at -1034705 (batch receipts for patient 202003); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILI™, actions taken at each visit, and measurement of BCVA).

183. Claims 8 and 21 require that a physician measure a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 52 weeks following the initial dose. The above chart demonstrates that at week 48 (*i.e.*, within 52 weeks), physicians measured a gain of 14 letters in patient 202003, which is a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁸⁰

184. Claim 9 requires that a physician measure a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 24 weeks following the initial dose. The above chart demonstrates that at week 20 (*i.e.*, within 24 weeks), physicians measured a gain of 12 letters in patient 202003, which is a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁸¹

185. Claims 10 and 17 require that a physician measure a gain of at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 52 weeks following the initial dose. The above chart demonstrates that at week 48 (*i.e.*, within 52 weeks), physicians measured a gain of 14 letters in patient

¹⁸⁰ MYL-AFL-BLA1059735, at -1067757 to -1067759 (showing BCVA scores at each visit for patient 202003); MYL-AFL-BLA1034645 at -1034705 (batch receipts for patient 202003); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

¹⁸¹ MYL-AFL-BLA1059735, at -1067757 to -1067759 (showing BCVA scores at each visit for patient 202003); MYL-AFL-BLA1034645 at -1034705 (batch receipts for patient 202003); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

202003, which is a gain of at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁸²

186. Claim 20 requires that a physician measure a gain of at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 24 weeks following the initial dose (claim 20). The above chart demonstrates that at week 20 (*i.e.*, within 24 weeks), physicians measured a gain of 12 letters in patient 202003, which is a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁸³

- **Patient 203007**

187. By way of another example, Mylan's BLA shows that a physician administered doses of 2mg YESAFILI™ at baseline and at weeks 4, 8, 12, 16, 24, 32, 40, and 48 to the patient with study number 203007 in Mylan's DME study.¹⁸⁴

¹⁸² MYL-AFL-BLA1059735, at -1067757 to -1067759 (showing BCVA scores at each visit for patient 202003); MYL-AFL-BLA1034645 at -1034705 (batch receipts for patient 202003); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILI™, actions taken at each visit, and measurement of BCVA).

¹⁸³ MYL-AFL-BLA1059735, at -1067757 to -1067759 (showing BCVA scores at each visit for patient 202003); MYL-AFL-BLA1034645 at -1034705 (batch receipts for patient 202003); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILI™, actions taken at each visit, and measurement of BCVA).

¹⁸⁴ MYL-AFL-BLA1034645 at -1034710 (batch receipts for patient 202007).

Site: 203

Subject Number	Age/Sex	Randomization Number	Treatment Group	Visit	Visit Number	Kit Number	Kit Status	Date the Kit was Dispensed	Label Lot Number of Kit
203006	66/F	112039	Eylea®	VISIT 15-WEEK 48	17	148504	RETURNED/DISC ROYED	19MAY2020	P183731
203007	44/M	111010	MYL-1701P	VISIT 1-BASELINE	2	460082	RETURNED/DISC ROYED	12JUN2019	P183731
				VISIT 4-WEEK 4	5	162673	RETURNED/DISC ROYED	09JUL2019	P183731
				VISIT 5-WEEK 8	6	496331	RETURNED/DISC ROYED	06AUG2019	P183731
				VISIT 6-WEEK 12	7	442522	RETURNED/DISC ROYED	28AUG2019	P183731
				VISIT 7-WEEK 16	8	489213	RETURNED/DISC ROYED	01OCT2019	P183731
				VISIT 9-WEEK 24	11	330304	RETURNED/DISC ROYED	26NOV2019	P183731
				VISIT 11-WEEK 32	13	475204	RETURNED/DISC ROYED	21JAN2020	P183731
				VISIT 13-WEEK 40	15	326304	RETURNED/DISC ROYED	24MAR2020	P183731
				VISIT 15-WEEK 48	17	236951	RETURNED/DISC ROYED	19MAY2020	P183731

Note: Kit numbers that couldn't be assigned to subject due to a mismatch in the databases are described in the CSR.

188. Thus, a physician administered to this patient a treatment regimen consistent with limitations (1pre) through (1c) of claim 1—*i.e.*, they administered one initial dose of 2 mg YESAFILI™ (aflibercept-jbvf) (at baseline), four secondary doses of 2 mg YESAFILI™ (aflibercept-jbvf) administered four weeks after the immediately preceding dose (at weeks 4, 8, 12, and 16), and four tertiary doses of 2 mg YESAFILI™ (aflibercept-jbvf) administered eight weeks after the immediately preceding dose (at weeks 24, 32, 40, and 48).¹⁸⁵

189. Furthermore, Mylan's BLA shows that a physician performed step (1d) of claim 1 with respect to patient number 203007, because physicians measured a gain in visual acuity in patient number 203007 within 52 weeks following the initial dose.¹⁸⁶ I have highlighted the measurements the physician took at weeks 24 and 52 to for frame of reference.

¹⁸⁵ MYL-AFL-BLA1034645 at -1034710 (batch receipts for patient 203007); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486 (protocol defining dosing of YESAFILI™, and actions taken at each visit).

¹⁸⁶ MYL-AFL-BLA1059735, at -1067765 to -1067767 (showing BCVA scores at each visit for patient 202007).

Listing 16.2.6.5b Best-Corrected Visual Acuity
Safety Analysis Set

Treatment Group: MYL-1701P

Subject Number	Age/ Sex	Visit	Date of Examination	Tester Initials	Eye	Letter Score			Low Vision Testing		
						4 M	1 M	BCVA Score	Finger Counting	Hand Movements	Light Perception
203005	56/M	VISIT 14-WEEK 44	21APR2020 07:00	MB	Study Eye	44		74			
				MB	Fellow Eye	60		90			
		VISIT 15-WEEK 48	19MAY2020 07:15	MB	Study Eye	47		77			
				MB	Fellow Eye	58		88			
		VISIT 16-WEEK 52/BOT/EOS	08JUN2020 07:25	MB	Study Eye	52		82			
				MB	Fellow Eye	60		90			
203007	44/M	SCREENING	05JUN2019 09:10	MB	Study Eye	22		52			
				MB	Fellow Eye	44		74			
		VISIT 1-BASELINE	12JUN2019 07:00	JB	Study Eye	22		52			
				JB	Fellow Eye	44		74			
		VISIT 4-WEEK 4	09JUL2019 07:40	JB	Study Eye	27		57			

FT = feet; M = meter; ND = Not done;

Listing 16.2.6.5b Best-Corrected Visual Acuity
Safety Analysis Set

Treatment Group: MYL-1701P

Subject Number	Age/ Sex	Visit	Date of Examination	Tester Initials	Eye	Letter Score			Low Vision Testing		
						4 M	1 M	BCVA Score	Finger Counting	Hand Movements	Light Perception
203007	44/M	VISIT 4-WEEK 4	09JUL2019 07:40	JB	Fellow Eye	43		73			
		VISIT 5-WEEK 8	06AUG2019 07:45	JB	Study Eye	27		57			
				JB	Fellow Eye	42		72			
		VISIT 6-WEEK 12	28AUG2019 07:40	MB	Study Eye	38		68			
				MB	Fellow Eye	38		68			
		VISIT 7-WEEK 16	01OCT2019 08:00	MB	Study Eye	43		73			
				MB	Fellow Eye	44		74			
		VISIT 8-WEEK 20	29OCT2019 07:35	JB	Study Eye	44		74			
				JB	Fellow Eye	43		73			
		VISIT 9-WEEK 24	26NOV2019 07:45	MB	Study Eye	45		75			
				MB	Fellow Eye	45		75			
		VISIT 10-WEEK 28	18DEC2019 08:50	MB	Study Eye	45		75			
				MB	Fellow Eye	46		76			

FT = feet; M = meter; ND = Not done;

Treatment Group: MYL-1701P

Subject Number	Age/ Sex	Visit	Date of Examination	Tester Initials	Eye	Letter Score		Low Vision Testing		
						4 M	1 M	BCVA Score	Finger Counting	Hand Movements
203007	44/M	VISIT 11-WEEK 32	21JAN2020 08:10	MB	Study Eye	41		71		
				MB	Fellow Eye	45		75		
		VISIT 12-WEEK 36	25FEB2020 06:40	MB	Study Eye	41		71		
				MB	Fellow Eye	45		75		
		VISIT 13-WEEK 40	24MAR2020 09:20	JB	Study Eye	42		72		
				JB	Fellow Eye	42		72		
		VISIT 14-WEEK 44	21APR2020 08:25	MB	Study Eye	43		73		
				MB	Fellow Eye	44		74		
		VISIT 15-WEEK 48	19MAY2020 07:45	MB	Study Eye	49		79		
				MB	Fellow Eye	50		80		
		VISIT 16-WEEK 52	10JUN2020 08:30	MB	Study Eye	47		77		

FT = feet; M = meter; ND = Not done;

190. Below, I have provided a table summarizing the gains a physician measured in patient 203007 below:

Week ¹⁸⁷	Visit Date ¹⁸⁸	2 mg of YESAFILITM administered? ¹⁸⁹	Gain Over Baseline According to ETDRS Letter Score ¹⁹⁰
Baseline	June 12, 2019	Yes	0 (by definition)
Week 4	July 9, 2019	Yes	5
Week 8	August 6, 2019	Yes	5
Week 12	August 28, 2019	Yes	16
Week 16	October 1, 2019	Yes	21

¹⁸⁷ MYL-AFL-BLA1059735, at -1067765 to -1067767 (showing BCVA scores at each visit for patient 202007); MYL-AFL-BLA1034645 at -1034685 (batch receipts for patient 203007).

¹⁸⁸ MYL-AFL-BLA1059735, at -1067725 to -1067727 (date of visit is same as date of study administration, per protocol); MYL-AFL-BLA1055435 at -1055481 to -1055486 (protocol per visit).

¹⁸⁹ MYL-AFL-BLA1034645 at -1034662 to -1034663 (batch receipts for patient 203007); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486 (protocol defining dosing of YESAFILITM, and actions taken at each visit).

¹⁹⁰ MYL-AFL-BLA1059735, at -1067765 to -1067767 (showing BCVA scores at each visit for patient 202007).

Week 20	October 29, 2019	No	22
Week 24	November 26, 2019	Yes	23
Week 28	December 18, 2019	No	23
Week 32	January 21, 2020	Yes	19
Week 36	February 25, 2020	No	19
Week 40	March 24, 2020	Yes	20
Week 44	April 21, 2020	No	21
Week 48	May 19, 2020	Yes	27
Week 52	June 10, 2020	No	25

191. Accordingly, a physician measured a gain in visual acuity within 52 weeks following the initial dose in patient No. 203007 in Mylan's DME study. By week 48 (*i.e.*, within 52 weeks), a physician measured a gain of 27 letters.

192. Other claims of the '572 patent place additional requirements on the measurement of visual acuity that the physician makes. The above BLA excerpts demonstrate that physicians made measurements meeting each of these requirements.¹⁹¹

193. In particular, Claim 2 requires that the gain the physician measures is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score. As the BLA excerpts I cited

¹⁹¹ MYL-AFL-BLA1059735, at -1067765 to -1067767 (showing BCVA scores at each visit for patient 202007); MYL-AFL-BLA1034645 at -1034710 (batch receipts for patient 202007); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, -1055488 (protocol defining dosing of YESAFILI™, actions taken at each visit, and measurement of BCVA).

above show, the measurements the physician performed on patient 203007 reported letter gains in visual acuity according to ETDRS letter score.¹⁹²

194. Claim 3 requires that a physician measure a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 52 weeks following the initial dose. The above chart demonstrates that at week 48 (*i.e.*, within 52 weeks), physicians measured a gain of 27 letters in patient 203007, which is a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁹³

195. Claim 4 requires that a physician measure a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 24 weeks following the initial dose. The above chart demonstrates that at week 20 (*i.e.*, within 24 weeks), physicians measured a gain of 22 letters in patient 203007, which is a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁹⁴

¹⁹² MYL-AFL-BLA1059735, at -1067765 to -1067767 (showing BCVA scores at each visit for patient 202007); MYL-AFL-BLA1034645 at -1034710 (batch receipts for patient 202007); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILI™, actions taken at each visit, and measurement of BCVA).

¹⁹³ MYL-AFL-BLA1059735, at -1067765 to -1067767 (showing BCVA scores at each visit for patient 202007); MYL-AFL-BLA1034645 at -1034710 (batch receipts for patient 202007); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILI™, actions taken at each visit, and measurement of BCVA).

¹⁹⁴ MYL-AFL-BLA1059735, at -1067765 to -1067767 (showing BCVA scores at each visit for patient 202007); MYL-AFL-BLA1034645 at -1034710 (batch receipts for patient 202007); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILI™, actions taken at each visit, and measurement of BCVA).

196. Claims 8 and 21 require that a physician measure a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 52 weeks following the initial dose. The above chart demonstrates that at week 48 (*i.e.*, within 52 weeks), physicians measured a gain of 27 letters in patient 203007, which is a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁹⁵

197. Claim 9 requires that a physician measure a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 24 weeks following the initial dose. The above chart demonstrates that at week 20 (*i.e.*, within 24 weeks), physicians measured a gain of 22 letters in patient 203007, which is a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁹⁶

198. Claims 10 and 17 require that a physician measure a gain of at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 52 weeks following the initial dose. The above chart demonstrates that at week 48 (*i.e.*, within 52 weeks), physicians measured a gain of 27 letters in patient

¹⁹⁵ MYL-AFL-BLA1059735, at -1067765 to -1067767 (showing BCVA scores at each visit for patient 202007); MYL-AFL-BLA1034645 at -1034710 (batch receipts for patient 202007); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

¹⁹⁶ MYL-AFL-BLA1059735, at -1067757 to -1067759 (showing BCVA scores at each visit for patient 202003); MYL-AFL-BLA1034645 at -1034710 (batch receipts for patient 202007); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILITM, actions taken at each visit, and measurement of BCVA).

203007, which is a gain of at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁹⁷

199. Claim 20 requires that a physician measure a gain of at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score within 24 weeks following the initial dose (claim 20). The above chart demonstrates that at week 20 (*i.e.*, within 24 weeks), physicians measured a gain of 22 letters in patient 203007, which is a gain of at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.¹⁹⁸

iii. Summary of Individual Patient Data

200. Mylan's data—submitted as part of its BLA—demonstrates that by marketing YESAFILI™ with its proposed labeling, direct infringement will occur. That is, Mylan's data demonstrate that it is more likely than not that one or more clinicians will, in fact, measure a gain in their patients' visual acuity within 52 weeks after administering the initial dose, as Claim 1 of the '572 Patent requires. Mylan's submission of this data to FDA (data that it touts to FDA and physicians alike as demonstrating the biosimilarity and clinical equivalence of Eylea® and YESAFILI™), in combination with the fact that its proposed labeling directs physicians to

¹⁹⁷ MYL-AFL-BLA1059735, at -1067765 to -1067767 (showing BCVA scores at each visit for patient 202007); MYL-AFL-BLA1034645 at -1034710 (batch receipts for patient 202007); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILI™, actions taken at each visit, and measurement of BCVA).

¹⁹⁸ MYL-AFL-BLA1059735, at -1067765 to -1067767 (showing BCVA scores at each visit for patient 202007); MYL-AFL-BLA1034645 at -1034710 (batch receipts for patient 202007); MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486, - 1055488 (protocol defining dosing of YESAFILI™, actions taken at each visit, and measurement of BCVA).

perform the other steps of the method (*i.e.*, limitations (1pre) through (1c), shows that Mylan knows such results will occur and specifically intends to induce this infringing activity.

iv. Clinical Experience

201. Mylan's proposed labeling instructs doctors to use YESAFILI™ in the same way they would use Eylea®, and that YESAFILI™ is clinically equivalent to Eylea® when used according to its label.¹⁹⁹ I have treated patients with DME using Eylea® in my own clinical practice, using an initial dose of 2 mg Eylea®, four secondary doses of 2 mg Eylea® four weeks after the immediately preceding dose, and then tertiary doses of 2 mg Eylea® eight weeks after the immediately preceding dose. I measure the BCVA of such patients before every injection, and I have measured BCVA gains within 52 weeks of the initial dose in such patients. I also frequently speak with other retinal specialists, and these conversations confirm that other physicians have done the same. On this basis, in combination with Mylan's instruction to doctors that YESAFILI™ is clinically equivalent to Eylea®, I conclude that if Mylan markets YESAFILI™ according to its proposed labeling, doctors will in fact perform limitations (1pre) through (1c) in order to treat DME, *and* measure BCVA gains according to ETDRS letter score.

202. In light of all of the above, Mylan recommends, encourages, and promotes infringement of claim 1 of the '572 patent by recommending, encouraging, and promoting a method of treating DME using YESAFILI™ that meets every limitation of claim 1. If Mylan markets YESAFILI™ with its proposed labeling, physicians will perform acts of direct infringement by treating DME using YESAFILI™ in a manner that meets every limitation of claim 1. Accordingly, the marketing of YESAFILI™ pursuant to Mylan's proposed labeling will induce infringement of claim 1 of the '572 patent.

¹⁹⁹ *Supra* section VI.D.2.

2) Mylan Induces Physicians to Measure a Gain in Visual Acuity in Patients to Whom They Administer YESAFILI™ to Treat DR

203. Mylan's phase III study was performed in patients with DME, but Mylan's proposed label for YESAFILI™ also instructs administration of YESAFILI™ to treat patients with DR. As I described above, *supra* Section III.D.3, Mylan's proposed labeling instructs doctors to treat patients with DR in a manner that practices the regimen recited in claim 1 of the '572 patent.

204. Mylan's proposed labeling also instructs doctors to use YESAFILI™ in the same way they would use Eylea®, and that YESAFILI™ is clinically equivalent to Eylea® when used according to its label.²⁰⁰ I have treated patients with DR using Eylea® in my own clinical practice, using an initial dose of 2 mg Eylea®, four secondary doses of 2 mg Eylea® four weeks after the immediately preceding dose, and then tertiary doses of 2 mg Eylea® eight weeks after the immediately preceding dose. I measure the BCVA of such patients before every injection, and I have measured BCVA gains within 52 weeks of the initial dose in such patients. I also frequently speak with other retinal specialists, and these conversations confirm that other physicians have done the same. On this basis, in combination with Mylan's instruction to doctors that YESAFILI™ is clinically equivalent to Eylea®, I conclude that if Mylan markets YESAFILI™ according to its proposed labeling, doctors will in fact perform limitations (1pre) through (1c) in order to treat DR, *and* measure BCVA gains according to ETDRS letter score.

205. In light of all of the above, Mylan recommends, encourages, and promotes infringement of claim 1 of the '572 patent by recommending, encouraging, and promoting a method of treating DR using YESAFILI™ that meets every limitation of claim 1. If Mylan

²⁰⁰ *Supra* section VI.D.2.

markets YESAFILI™ with its proposed labeling, physicians will perform acts of direct infringement by treating DR using YESAFILI™ in a manner that meets every limitation of claim

1. Accordingly, the marketing of YESAFILI™ pursuant to Mylan’s proposed labeling will induce infringement of claim 1 of the ’572 patent.

3) Mylan Induces Physicians to Measure a Gain in Visual Acuity in Patients to Whom They Administer YESAFILI™ to Treat AMD

206. Mylan’s phase III study was performed in patients with DME, but Mylan’s proposed label for YESAFILI™ also instructs administration of YESAFILI™ to treat patients with AMD. As I described above, *supra* Section III.D.3, Mylan’s proposed labeling instructs doctors to treat patients with AMD in a manner that practices the regimen recited in claim 1 of the ’572 patent.

207. Mylan’s proposed labeling also instructs doctors to use YESAFILI™ in the same way they would use Eylea®, and that YESAFILI™ is clinically equivalent to Eylea® when used according to its label.²⁰¹ I have treated patients with AMD using Eylea® in my own clinical practice, using an initial dose of 2 mg Eylea®, two secondary doses of 2 mg Eylea® four weeks after the immediately preceding dose, and then tertiary doses of 2 mg Eylea® eight weeks after the immediately preceding dose. I measure the BCVA of such patients before every injection, and I have measured BCVA gains within 52 weeks of the initial dose in such patients. I also frequently speak with other retinal specialists, and these conversations confirm that other physicians have done the same. On this basis, in combination with Mylan’s instruction to doctors that YESAFILI™ is clinically equivalent to Eylea®, I conclude that if Mylan markets

²⁰¹ *Supra* section VI.D.2.

YESAFILI™ according to its proposed labeling, doctors will in fact perform limitations (1pre) through (1c) in order to treat AMD, *and* measure BCVA gains according to ETDRS letter score.

208. In light of all of the above, Mylan recommends, encourages, and promotes infringement of claim 1 of the '572 patent by recommending, encouraging, and promoting a method of treating AMD using YESAFILI™ that meets every limitation of claim 1. If Mylan markets YESAFILI™ with its proposed labeling, physicians will perform acts of direct infringement by treating AMD using YESAFILI™ in a manner that meets every limitation of claim 1. Accordingly, the marketing of YESAFILI™ pursuant to Mylan's proposed labeling will induce infringement of claim 1 of the '572 patent.

4) Mylan's Incorrect Interpretation of Limitation (1d)

209. I am informed by counsel that Mylan may disagree with my understanding of limitation (1d), based on Mylan's statement at the parties' claim construction hearing on January 24, 2023. In particular, I understand Mylan may argue that limitation (1d) is not a step of the method of claim 1, but rather is satisfied whenever a patient achieves a visual acuity gain within 52 weeks of the patient's initial YESAFILI™ dose, even if no physician ever measures that result.

210. I disagree with Mylan's interpretation of the claim, as the POSA would understand it to require a step of measuring. However, even if I were instructed to apply Mylan's interpretation of the claim, my conclusion about whether Mylan induces infringement of claim 1 of the '572 patent would not be altered. Under Mylan's interpretation, a physician need only perform limitations (1pre) through (1c) to directly infringe claim 1 of the '572 patent. As I have explained above, if Mylan markets YESAFILI™ in accordance with its proposed labeling, physicians will perform limitations (1pre) through (1c) in order to treat DME with respect to a patient who experiences a gain in visual acuity within 52 weeks of the initial dose, and Mylan's

label recommends, encourages, and promotes this conduct. As the data above in Sections VI.D.3.e.1.i & ii demonstrate, Mylan specifically intends at least one physician will perform these method steps with respect to a patient who experiences a gain in visual acuity within week 52 of the initial dose, and it is more likely than not that such acts will in fact occur.

5) Claim 1 Conclusion

211. For the reasons explained above, if Mylan markets YESAFILI™ according to its proposed labeling, physicians will in fact perform the method of Claim 1.

212. By marketing YESAFILI™ according to its approved labeling, which instructs clinicians to use YESAFILI™ in the same manner as Eylea® and in the manner recited in claim 1, Mylan specifically intends such infringement to occur and knows such infringement will occur. Mylan therefore induces infringement of claim 1 of the '572 patent.

4. Claim 2

213. Claim 2 of the '572 patent recites:

2. The method of claim 1 wherein the patient achieves a gain in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

214. I understand that claim 2 depends from claim 1. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 1 of the '572 patent. I incorporate the analysis of claim 1 as though fully set forth herein.

215. Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 1 *and* the further limitation of claim 2, "wherein the patient achieves a gain in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score."

a) BCVA

216. BCVA—best corrected visual acuity—is a measure of the best vision an eye can achieve using corrective lenses, like glasses or contacts. It is a concept that is used in my everyday clinical practice, where I measure the effect of angiogenic eye disorders (or their treatment) on my patients' vision, and I need a standard by which to record the results and track changes over time.

217. To understand the concept of BCVA in clinical practice, it is important to understand that there are different problems that can affect a patient's vision. "Refractive errors" are the typical nearsightedness or farsightedness caused by the shape of a patient's eye, which can be alleviated using glasses or contact lenses. This is very different than the blurry or impaired vision caused by blood vessel growth or leakage in angiogenic eye disorders. The POSA would understand BCVA to have a day-to-day conceptual and practical meaning for use in clinical practice. BCVA is a concept that a POSA uses when following a patient during any routine visit, and in particular when administering anti-VEGF therapies. The use of the BCVA concept directs that the POSA measure an AMD/DME/DR/RVO patient's vision with his or her corrective lenses, because the POSA treating a patient for angiogenic eye disorders would want to measure any changes that occur in that patient's vision beyond any uncorrected refractive errors. This is what I do in my own clinical practice. Furthermore, to implement the BCVA concept, the POSA will, at times, use pinhole vision, beyond a patient's prescription lens, to ensure that the patient's corrective vision cannot be improved. Pinhole vision will at times overcome any additional refractive error and provide better visual acuity metrics. In this case, it is not uncommon then for the POSA to either recommend additional changes in that patient's glasses and/or contact lenses or in the clinic provide some additional refractive correction. Again, this reflects my own practice. When I have treated patients with angiogenic eye disorders

using an anti-VEGF agent in clinical practice, I have always employed the concept of BCVA. That is because I want to understand whether anti-VEGF agents are adequately controlling my patients' disease, and these changes are best understood when they are measured without the confounding or obscuring effects of refractive errors. The POSA would have had the same understanding. To that end, when I have treated patients using Eylea®, I have, at times, measured and recorded vision that reflects BCVA, so I can understand whether their AMD, DME, DR, or RVO is responding to treatment appropriately.

218. I am informed that Mylan argues BCVA is a concept or measurement only used in clinical trials, not in clinical practice, and that "visual acuity" (rather than *best corrected* visual acuity) is what is measured during normal visits to physicians. This is simply untrue. For all the reasons I described above, *supra* Section III, I have actively measured and tracked changes in my patients' visual acuity when I treat them with anti-VEGF agents like Eylea®. And because I am interested in angiogenic, rather than refractive, changes, I will employ the concept of BCVA to actively measure and record changes in *best corrected* visual acuity in my clinical practice when I treat patients using anti-VEGF agents. I also frequently speak with other retinal specialists regarding standards of care, and these conversations confirm that other physicians do the same—they actively measure and track the *best corrected* visual acuity of patients to whom they administer anti-VEGF agents.²⁰² The POSA would not have understood the concept of BCVA to have been limited to clinical trials.

²⁰²See Natalia F. Callaway, M.D., *Outcomes of Pars Plana Vitrectomy for Macular Hole in Patients with Uveitis*, in The Journal of Retinal and Vitreous Diseases Vol. 38 No. 9, S42 (2018) ("Callaway"), (referring to "Snellen best-corrected visual acuity (BCVA)" as one of several baseline characteristics measured as part of a "standard clinical examination."); see Pearse A. Keane, MRCPth, *Effect of Ranibizumab Retreatment Frequency on Neurosensory Retinal Volume in Neovascular AMD*, in The Journal of Retinal and Vitreous Diseases Vol. 29 No. 5,

b) ETDRS Letter Score

1) ETDRS Letter Scores Need Not Be Measured Using ETDRS Charts or Protocols

219. Physicians can measure a patient's change in BCVA using many different scales.

For example, a physician may measure a patient's BCVA using different systems—common ones include the Early Treatment Diabetic Retinopathy Score (“ETDRS”) Letter Scores and Snellen. Once BCVA has been measured, physicians can convert scores from one scale or unit to another²⁰³—for example, if a patient has a Snellen score of 20/200, a physician would understand that patient has an ETDRS letter score of at least about 35 letters. Tables are available in the literature equating between ETDRS and Snellen, typically by converting both values to a “LogMAR” score.²⁰⁴ The table below shows conversion of Snellen scores to LogMAR scores, and was available in a 2009 clinical ophthalmology textbook.²⁰⁵

593(2009) (retrospective study where patients “best-corrected Snellen visual acuity” was measured.)

²⁰³ MYL-AFL0089404 at -0089407 (noting patients in Mylan’s Phase III study comparing YESAFILTM to Eylea® involved admitted patients with “best corrected visual acuity of 73 to 38 ETDRS letters, or Snellen equivalent of 20/40 to 20/200”); *see* Ganapathi Tr. 92:18–21 (“Q. What are the other methods that can be used to measure best corrected visual acuity? A. Instead of ETDRS chart, you can use Snellen chart.”), Ganapathi Tr. at 96:11–16 (“Q. What is a Snellen equivalent? A. There is a conversion chart where ETDRS letter range is compared with or could be equivalence to Snellen’s scope. This is an equivalence to Snellen scope because Snellen’s is more popular many times in practice.”).

²⁰⁴Clinical Optics at 110; Moke at 198.

²⁰⁵Clinical Optics at 110.

110 • Clinical Optics

Table 3-2 Visual Acuity Conversion Chart

Feet	Snellen Fraction Meters	4-Meter Standard	Minimum Angle of Resolution	LogMAR	Decimal Notation
20/10	6/3	4/2	0.50	-0.30	2.00
20/15	6/4.5	4/3	0.75	-0.10	1.50
20/20	6/6	4/4	1.00	0.00	1.00
20/25	6/7.5	4/5	1.25	0.10	0.80
20/30	6/9	4/6	1.50	0.18	0.70
20/40	6/12	4/8	2.00	0.30	0.50
20/50	6/15	4/10	2.50	0.40	0.40
20/60	6/18	4/12	3.00	0.48	0.30
20/80	6/24	4/16	4.00	0.60	0.25
20/100	6/30	4/20	5.00	0.70	0.20
20/120	6/36	4/24	6.00	0.80	
20/150	6/45	4/32	7.50	0.88	0.13
20/200	6/60	4/40	10.00	1.00	0.10
20/400	6/120	4/80	20.00	1.30	0.05

LogMAR scores are readily convertible to ETDRS Letter scores, via a formula ($\text{logMAR} = 1.7 - (.02)(\text{letter score})$).²⁰⁶ Tables in the literature show conversions directly from Snellen to ETDRS Letter scores.²⁰⁷

²⁰⁶ Moke at 198.

²⁰⁷ Moke at 197 (Table 1).

TABLE 1. Conversions Between Letter, LogMAR, and Snellen Visual Acuity Scores

Letter Score	LogMAR Value	Snellen Equivalent
5	1.6	20/800
10	1.5	20/640
15	1.4	20/500
20	1.3	20/400
25	1.2	20/320
30	1.1	20/250
35	1.0	20/200
40	0.9	20/160
45	0.8	20/125
50	0.7	20/100
55	0.6	20/80
60	0.5	20/63
65	0.4	20/50
70	0.3	20/40
75	0.2	20/32
80	0.1	20/25
85	0.0	20/20
90	-0.1	20/15
95	-0.2	20/12

LogMAR = logarithm of the minimal angle of resolution.

220. As I explained above, claim 1 of the '572 patent requires that physicians measure a gain in a patient's visual acuity. Claim 2 requires that physicians measure "a gain in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score." To the extent Mylan argues that this claim requires that physicians perform the measurement *using* an ETDRS chart or protocol only, I do not agree, and the POSA would not understand claim 2 to contain such a requirement. An ETDRS letter score is a value (like temperature), not a protocol, and an ETDRS letter score does not imply use of the ETDRS protocol and the claims, on their face do not reference the ETDRS protocol. Just as temperature in Celsius can be measured using a thermometer that reports either Celsius or Fahrenheit values, ETDRS letter scores can be measured in a number of ways, including via a visual acuity chart (*i.e.*, Snellen) that produces values interpretable as ETDRS letter scores.

221. For example, consider a method that required doctors to measure an increase in temperature in a patient wherein the increase is according to degrees Celsius. A doctor who

measures a patient's temperature to be 98.6 degrees Fahrenheit on Day 1 and 103 degrees Fahrenheit on Day 2 has performed this method, because that physician has measured an increase in temperature of 2.4 degrees Celsius. This is true because, as any physician would understand, the conversion from Fahrenheit to Celsius is $^{\circ}\text{C} = (^{\circ}\text{F}-32) \times 5/9$. Therefore, 98.6 degrees Fahrenheit is equivalent to 37 degrees Celsius, and 103 degrees Fahrenheit is equivalent to 39.4 degrees Celsius. The same is true here: a physician who measures a patient to have a Snellen score of 20/200 (which the POSA would understand is equivalent to an ETDRS letter score of at least 35) on Day 1 and measures a patient to have a Snellen score of 20/160 on Day 2 (which the POSA would understand is equivalent to an ETDRS letter score of at least 40), has measured a gain according to ETDRS equivalent to about 5 letters ETDRS.²⁰⁸

222. For the reasons I described in Section VI.D.3.a and VI.D.4.a above (and incorporate here by reference), Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce physicians to perform the active step of measuring gains in BCVA after administering the regimen of YESAFILI™ recited in claim 1. Upon marketing of YESAFILI™ in accordance with its proposed labeling, physicians will in fact perform the active step of measuring gains in BCVA after administering the regimen of YESAFILI™ recited in claim 1. Because a BCVA gain, however measured, can be quantified as according to ETDRS letter score, such physicians will perform each step of the method of claim 2 of the '572 patent. Mylan recommends, encourages, and promotes this result by virtue of marketing YESAFILI™ according to its proposed labeling, and will therefore induce infringement of claim 2.

²⁰⁸ Moke at 197 (Table 1).

**2) Mylan Induces Literal Infringement of Claim 2
Even If Claim 2 Requires Measurement Using the
ETDRS Chart**

223. Even assuming, *arguendo*, that claim 2 requires physicians to measure a gain in BCVA and to *perform that measurement using an ETDRS chart* (and to be clear, I disagree that the POSA would understand claim 2 in that way)—it is still my opinion that Mylan’s marketing of YESAFILI™ according to its proposed labeling will induce literal infringement of claim 2. Simply put, some physicians perform BCVA measurements using ETDRS charts to measure BCVA in their clinical practice. I have done so myself, and I am aware of colleagues who have done the same. If Mylan markets YESAFILI™ in accordance with its proposed labeling, which recommends, encourages, and promotes use of the method of claim 1, some physicians will in fact measure gains in BCVA using an ETDRS chart. Mylan recommends, encourages, and promotes this result by virtue of its proposed labeling for YESAFILI™ and its knowledge of clinical practice.

3) Mylan Induces Infringement of Claim 2 Under the Doctrine of Equivalents If Claim 2 Requires Measurement Using the ETDRS Chart or Using an ETDRS Protocol

224. Alternatively, Mylan’s marketing of YESAFILI™ according to its proposed labeling will induce infringement of claim 2 under the doctrine of equivalents even if claim 2 were interpreted to require physicians measure BCVA gains using an ETDRS chart or a more detailed ETDRS protocol. The physician measures the same visual acuity gain regardless of which chart or protocol the physician uses, and may freely convert between Snellen and ETDRS letter score results. Moreover, measuring BCVA using a Snellen chart performs substantially the same function (*i.e.*, measuring the patient’s response to treatment in terms of BCVA), in substantially the same way (*i.e.*, using an eye chart and refractive lenses), to achieve substantially the same result (*i.e.*, a measurement of the patient’s BCVA that can be used to make treatment

decisions) as measuring BCVA using an ETDRS chart or an ETDRS protocol. This is evidenced by the fact that physicians freely convert between Snellen and ETDRS values, as I have described above.

c) Claim 2 and Its Dependent Claims Are Not Limited to the Clinical Trial Setting

225. I am informed that Mylan argues that claim 2 cannot be practiced outside the confines of a clinical trial, because claim 2 refers to BCVA and to ETDRS Letter Scores. Simply put, this is not how the POSA would understand claim 2. First, BCVA and ETDRS Letter Scores are concepts that apply in patient practice as well as in clinical trials. As I explained above, I measure patients' BCVA in my clinical practice, and every time I do I produce a value that can be converted to and/or recorded as an ETDRS letter score. Furthermore, I have personally used ETDRS charts to measure BCVA in my clinical experience.

d) Claim 2 Conclusion

226. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform the method of claim 2.

227. Mylan's proposed labeling encourages, recommends, and promotes performance of the method of claim 2 by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 2, and specifically intends this infringing activity.

228. In the event the Court interprets this claim to not require the physician to measure a gain in visual acuity, I likewise conclude that Mylan would induce infringement of this claim, since Mylan induces infringement of the method of limitations (1pre) through 1(c) of claim 1, as I describe above, and Mylan specifically intends that at least one physician will perform these

method steps with respect to a patient who experiences a gain in visual acuity within week 52 of the initial dose, and it is more likely than not that such acts will in fact occur.

229. I also incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix C as though set forth fully herein.

5. Claim 3

230. Claim 3 of the '572 patent recites:

3. The method of claim 2 wherein the patient gains at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

231. I understand that claim 3 depends from claim 2, which depends from claim 1. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 2 of the '572 patent. I incorporate the analysis of claim 2 as though fully set forth herein.

232. Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 2 *and* the further limitation of claim 3, "wherein the patient gains at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score."

233. As I explained above in Section VI.D.3.e.1, Mylan reported the results of its Phase III clinical trial in patients with DME using YESAFILI™ to the FDA, as part of its BLA, and to doctors at conferences like AAO.²⁰⁹ I incorporate that analysis as though set forth herein. That data demonstrates that when YESAFILI™ is administered according to the method of claim

²⁰⁹ *Supra* Section VI.D.3.e.1.

1, patients gained more than 7 letters of BCVA according to ETDRS Letter Score within 52 weeks of the initial dose.²¹⁰ In particular, Mylan's clinical study reported that doctors measured a gain of more than 10 letters in 57.4% of patients to whom they administered YESAFILI™ according to Mylan's study protocol, and 55.9% of patients to whom they administered YESAFILI™ received one initial dose of 2 mg YESAFLILI™ (aflibercept-jbvf), followed by four secondary doses of 2 mg YESAFILI™ (aflibercept-jbvf) administered approximately four weeks after the immediately preceding dose, followed by three tertiary doses of 2 mg YESAFILI™ (aflibercept-jbvf) administered approximately eight weeks after the immediately preceding dose.²¹¹ Furthermore, in Section VI.D.3.e.1.ii above, I identified several individual instances in which physicians administered that regimen of YESAFILI™ and measured a gain of at least 7 letters BCVA according to ETDRS within 52 weeks of the initial dose.²¹² I likewise incorporate that analysis as though set forth herein.

234. This data, which Mylan has presented both to the FDA as part of its BLA and to doctors at conferences,²¹³ demonstrates that if Mylan markets YESAFILI™ according to its proposed labeling, physicians who have performed the method of claim 2 will also measure a BCVA gain of at least 7 letters according to ETDRS letter score within 52 weeks of the initial dose, as claim 3 requires.

²¹⁰ *Supra* Section VI.D.3.e.1.i.

²¹¹ MYL-AFL-BLA1056844 at -6950; MYL-AFL0089391 at -89399.

²¹² *Supra* Section VI.D.3.e.1.ii.

²¹³ MYL-AFL-BLA1056844 at -6950; MYL-AFL0089391 at -89399.

235. Mylan's proposed labeling instructs doctors to use YESAFILI™ in the same way they would use Eylea®, and that YESAFILI™ is clinically equivalent to Eylea® when used according to its label.²¹⁴ As I described above in Section VI.D.3, Mylan's proposed labeling instructs doctors to treat patients with DME in a manner that practices the regimen recited in claim 1 of the '572 patent. I incorporate that analysis herein by reference. Mylan's proposed labeling also instructs doctors to use YESAFILI™ in the same way they would use Eylea®, and that YESAFILI™ is clinically equivalent to Eylea® when used according to its label.²¹⁵ I have treated patients with DME using Eylea® in my own clinical practice, using an initial dose of 2 mg Eylea®, four secondary doses of 2 mg Eylea® four weeks after the immediately preceding dose, and then tertiary doses of 2 mg Eylea® eight weeks after the immediately preceding dose. I measure the BCVA of such patients before every injection, and I have measured BCVA gains of at least 7 letters according to ETDRS letter score in such patients. I also frequently speak with other retinal specialists, and these conversations confirm that other physicians have done the same. On this basis, in combination with Mylan's instruction to doctors that YESAFILI™ is clinically equivalent to Eylea® and the clinical data recited above, I conclude that if Mylan markets YESAFILI™ according to its proposed labeling, doctors will perform the method of claim 2 in order to treat DME, and will perform the step of measuring BCVA gains of at least 7 letters according to ETDRS letter score in such patients, as claim 3 requires.

236. Mylan's phase III study was performed in patients with DME, but Mylan's proposed label for YESAFILI™ also instructs administration of YESAFILI™ to treat patients with AMD. As I described above in Section III.D.3, Mylan's proposed labeling instructs doctors

²¹⁴ *Supra* Section VI.D.2.

²¹⁵ *Supra* Section VI.D.2.

to treat patients with AMD in a manner that practices the regimen recited in claim 1 of the '572 patent. I incorporate that analysis herein by reference. Mylan's proposed labeling also instructs doctors to use YESAFILI™ in the same way they would use Eylea®, and that YESAFILI™ is clinically equivalent to Eylea® when used according to its label.²¹⁶ I have treated patients with AMD using Eylea® in my own clinical practice, using an initial dose of 2 mg Eylea®, two secondary doses of 2 mg Eylea® four weeks after the immediately preceding dose, and then tertiary doses of 2 mg Eylea® eight weeks after the immediately preceding dose. I measure the BCVA of such patients before every injection, and I have measured BCVA gains of at least 7 letters according to ETDRS Letter Score in such patients. I also frequently speak with other retinal specialists, and these conversations confirm that other physicians have done the same. On this basis, in combination with Mylan's instruction to doctors that YESAFILI™ is clinically equivalent to Eylea®, I conclude that if Mylan markets YESAFILI™ according to its proposed labeling, doctors will in fact perform the method of claim 2 to treat AMD, *and* measure BCVA gains of at least 7 letters according to ETDRS letter score in such patients.

237. As I described above in Section VI.D.3, Mylan's proposed labeling instructs doctors to treat patients with DR in a manner that practices the regimen recited in claim 1 of the '572 patent. I incorporate that analysis herein by reference. Mylan's proposed labeling also instructs doctors to use YESAFILI™ in the same way they would use Eylea®, and that YESAFILI™ is clinically equivalent to Eylea® when used according to its label.²¹⁷ I have treated patients with DR using Eylea® in my own clinical practice, using an initial dose of 2 mg Eylea®, four secondary doses of 2 mg Eylea® four weeks after the immediately preceding dose,

²¹⁶ *Supra* Section VI.D.2.

²¹⁷ *Supra* Section VI.D.2.

and then tertiary doses of 2 mg Eylea® eight weeks after the immediately preceding dose. I measure the BCVA of such patients before every injection, and I have measured BCVA gains of at least 7 letters according to ETDRS Letter Score in such patients. I also frequently speak with other retinal specialists, and these conversations confirm that other physicians have done the same. On this basis, in combination with Mylan's instruction to doctors that YESAFILI™ is clinically equivalent to Eylea® and the clinical data recited above, I conclude that if Mylan markets YESAFILI™ according to its proposed labeling, doctors will perform the method of claim 2 in order to treat DR, and will perform the step of measuring BCVA gains of at least 7 letters according to ETDRS letter score in such patients, as claim 3 requires.

238. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 2 and measure a gain of at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score in the treated patient, as claim 3 requires. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 2 *and* measure BCVA gains of at least 7 letters according to ETDRS letter score in the treated patients as claim 4 requires, and Mylan specifically intends this infringing activity.

239. In light of the above, if Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform the method of claim 3.

240. Mylan's proposed labeling encourages, recommends, and promotes performance of claim 3 by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will administer YESAFILI™ to treat AMD, DR, and DME using the method of claim 3, and specifically intends this infringing activity. Mylan therefore induces infringement of claim 3 of the '601 patent.

241. I also incorporate by reference my analysis with respect to Claim 2 above with respect to BCVA, ETDRS, and the fact that such claims are not limited to clinical trials.²¹⁸ That analysis applies equally to this claim. For the same reasons I explained with respect to claim 2, the POSA would not understand this claim to require measurement of a gain of 7 letters BCVA within 52 weeks of the initial dose using an ETDRS chart; the POSA would instead understand this claim to require measuring a gain in BCVA that is equivalent to 7 letters BCVA according ETDRS letter score, and would understand that such a gain can be measured by performing any appropriate visual acuity testing protocol (e.g., Snellen).²¹⁹ Regardless, even if this claim were interpreted to require measurement using an ETDRS chart, it is still my opinion that Mylan induces infringement of this claim for the same reasons I explained with respect to claim 2 above—namely, because physicians do in fact use ETDRS charts in clinical practice to measure visual acuity gain (I myself have done so), and physicians will use ETDRS charts to measure gains of 7 letters BCVA within 52 weeks of the initial dose according to EDTRS if Mylan markets YESAFILI™ according to its proposed labeling²²⁰ Furthermore, even were this claim interpreted to require use of an ETDRS chart, or an ETDRS protocol, to measure visual acuity, Mylan would induce infringement of this claim under the doctrine of equivalents, for all the reasons I explained above with respect to claim 2.²²¹ Again, for all the reasons I explained with respect to claim 2, this claim is not limited to the performance of its method in clinical trials, and

²¹⁸ *Supra* Sections VI.D.4.a, VI.D.4 b, and VI.D.4c.

²¹⁹ *Supra* Section VI.D.4.b.1.

²²⁰ *Supra* Section VI.4.b.2.

²²¹ *Supra* Section VI.4.b.3.

the POSA would not understand the reference to ETDRS and BCVA to mean that the method of this claim can only be performed during clinical trials.²²² Finally, in the event the Court interprets this claim to not require the physician to perform the step of measuring a gain in visual acuity, I likewise conclude that Mylan would induce infringement of this claim, because if Mylan markets YESAFILI™ in accordance with its approved labeling, at least one physician will perform the steps of claim 1 with respect to a patient who experiences a gain in BCVA according to ETDRS letter score within 52 weeks of the initial dose, and Mylan's proposed labeling recommends, encourages and promotes this conduct.

242. I also incorporate by reference my analysis of claim 3 in the claim charts appended hereto as Appendix C as though set forth fully herein.

6. Claim 4

243. Claim 4 of the '572 patent recites:

4. The method of claim 3 wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose.

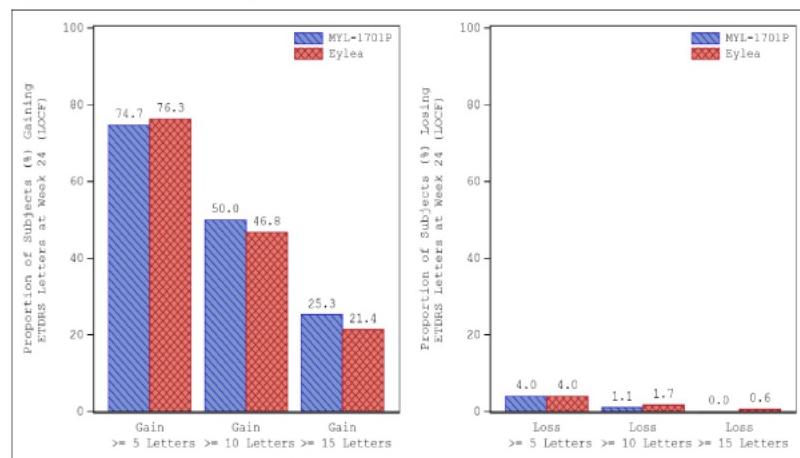
244. I understand that claim 4 depends from claim 3, which depends from claim 2, which depends from claim 1. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 3 of the '572 patent. I incorporate the analysis of claim 3 as though fully set forth herein.

245. Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 3 *and* the further limitation of claim 4, "wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose."

²²² *Supra* Section VI.D.4.d.

246. Mylan also reported the week 24 results of its Phase III clinical study in patients with DME using YESAFILI™ to the FDA, as part of its BLA.²²³ That data demonstrates that when YESAFILI™ is administered according to the method of claim 1, patients gained more than 7 letters of BCVA according to ETDRS Letter Score within 24 weeks of the initial dose. In particular, Mylan's clinical study reported that doctors measured a gain of more than 10 letters in 50.0% of patients to whom they administered YESAFILI™ according to Mylan's study protocol.²²⁴

Figure 9: Proportion of Subjects Who Gained or Lost ≥5, ≥10 or ≥15 Letters, at Week 24



Source: Figure 14.2.2.4.1a; Listing 16.2.6.5a

247. Furthermore, I have reviewed the individual patient efficacy results, and have identified several patients to whom doctors administered YESAFILI™ in accordance with the method of claim 1 and then measured a gain of more than 7 letters BCVA according to ETDRS

²²³ MYL-AFL-BLA0552809.

²²⁴ MYL-AFL-BLA1056844 at -6950; MYL-AFL0089391 at -89399.

within 24 weeks of the initial dose.²²⁵ Examples include patients 110003, 110012, 117013, 202003, and 203007.²²⁶

248. This data, which Mylan has presented to the FDA as part of its BLA,²²⁷ demonstrates that if Mylan markets YESAFILI™ according to its proposed labeling, doctors will in fact perform the method of claim 3 to treat DME, *and* measure a BCVA gain of at least 7 letters ETDRS within 24 weeks of the initial dose (*i.e.*, claim 4).

249. Mylan's phase III study was performed in patients with DME, but Mylan's proposed label for YESAFILI™ also instructs administration of YESAFILI™ to treat patients with AMD. As I described above, *supra* Section VI.D.3, Mylan's proposed labeling instructs doctors to treat patients with AMD in a manner that practices the regimen recited in claim 1 of the '572 patent. Mylan's proposed labeling also instructs doctors to use YESAFILI™ in the same way they would use Eylea®, and that YESAFILI™ is clinically equivalent to Eylea® when used according to its label.²²⁸ I have treated AMD patients using Eylea® in my own clinical practice, using an initial dose of 2 mg Eylea®, two secondary doses of 2 mg Eylea® two weeks after the immediately preceding dose, and then tertiary doses of 2 mg Eylea® four weeks after the immediately preceding dose. I measure the BCVA of such patients before every injection, and I have measured BCVA gains of 7 letters according to ETDRS Letter Score in such patients within 24 weeks of the initial dose. On this basis, in combination with Mylan's instruction to doctors that YESAFILI™ is clinically equivalent to Eylea®, I conclude that if Mylan markets

²²⁵ *Supra* Section VI.D.e.1.ii.

²²⁶ *Supra* Section VI.D.e.1.ii.

²²⁷ MYL-AFL-BLA1056844 at -6950; MYL-AFL0089391 at -89399.

²²⁸ *Supra* section VI.D.2.

YESAFILI™ according to its proposed labeling, doctors will in fact perform the method of claim 3 to treat AMD, *and* measure a BCVA gain of at least 7 letters ETDRS within 24 weeks of the initial dose.

250. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the the method of claim 3 *and* the further limitation of claim 4, “wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose.” Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 3 *and* the further limitation of claim 4, “wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose”, and specifically intends this infringing activity of claim 4.

251. I also incorporate by reference my analysis with respect to claim 2 above with respect to BCVA, ETDRS, and the fact that such claims are not limited to clinical trials.²²⁹ That analysis applies equally to this claim. For the same reasons I explained with respect to claim 2, the POSA would not understand this claim to require measurement of a gain of 7 letters BCVA within 24 weeks of the initial dose using an ETDRS chart; the POSA would instead understand this claim to require measuring a gain in BCVA that is equivalent to 7 letters BCVA according ETDRS letter score, and would understand that such a gain can be measured by performing any appropriate visual acuity testing protocol (e.g., Snellen).²³⁰ Regardless, even were this claim interpreted to require measurement using an ETDRS chart, it is still my opinion that Mylan induces infringement of this claim for the same reasons I explained with respect to claim 2 above—namely, because physicians do in fact use ETDRS charts in clinical practice to measure

²²⁹ *Supra* Sections VI.D.4.a, VI.D.4 b, and VI.D.4c.

²³⁰ *Supra* Section VI.D.4.b.1.

visual acuity gain (I myself have done so), and physicians will use ETDRS charts to measure gains of 7 letters BCVA within 24 weeks of the initial dose according to EDTRS if Mylan markets YESAFILI™ according to its proposed labeling, just as Mylan's proposed labeling recommends, encourages, and promotes.²³¹ Furthermore, even were this claim interpreted to require use of an ETDRS chart, or an ETDRS protocol, to measure visual acuity, Mylan would induce infringement of this claim under the doctrine of equivalents, for all the reasons I explained above with respect to claim 2.²³² Again, for all the reasons I explained with respect to claim 2, this claim is not limited to the performance of its method in clinical trials, and the POSA would not understand the reference to ETDRS and BCVA to mean that the method of this claim can only be performed during clinical trials.²³³ In the event the Court interprets this claim to not require the physician to perform the step of measuring a gain in visual acuity, I likewise conclude that Mylan would induce infringement of this claim, because if Mylan markets YESAFILI™ in accordance with its approved labeling, at least one physician will perform the steps of claim 1 with respect to a patient who experiences a gain in BCVA according to ETDRS letter score within 52 weeks of the initial dose, and Mylan's proposed labeling recommends, encourages and promotes this conduct.

252. I also incorporate by reference my analysis of claim 4 in the claim charts appended hereto as Appendix C as though set forth fully herein.

7. Claim 5

253. Claim 5 of the '572 patent recites:

²³¹ *Supra* Section VI.4.b.2.

²³² *Supra* Section VI.4.b.3.

²³³ *Supra* Section VI.D.4.d.

5. The method of claim 3 wherein only two secondary doses are administered to the patient.

254. I understand that claim 5 depends from claim 3, which depends from claim 2, which depends from claim 1. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 3 of the '572 patent. I incorporate the analysis of claim 3 as though fully set forth herein.

255. Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 3 *and* the further limitation of claim 5, "wherein only two secondary doses are administered to the patient."

256. It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to treat AMD by administering an "initial" dose of 2 mg Eylea® (aflibercept), followed by two "secondary" doses of 2 mg Eylea® (aflibercept), followed by one or more "tertiary" doses of 2 mg Eylea® (aflibercept).

257. Specifically, the Eylea® label instructs physicians to treat the angiogenic eye disorder of AMD by administering 2 mg of Eylea® (aflibercept) "by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)."

258. Accordingly, the Eylea® label instructs physicians to treat the angiogenic eye disorder AMD by administering a single "initial" dose of 2 mg aflibercept, followed by a "secondary" dose of 2 mg Eylea® (aflibercept) four weeks later, followed by another "secondary" dose of 2 mg Eylea® (aflibercept) four weeks after that, followed by a tertiary dose of 2 mg Eylea® (aflibercept) eight weeks after that (*i.e.*, eight weeks after the second,

“secondary” dose), followed by additional “tertiary” doses of 2 mg Eylea® at 8 week intervals thereafter.

259. In other words, when the Eylea® label instructs a physician to administer 2 mg Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months”, before switching to dosing once every 8 weeks, it expressly instructs physicians to administer “a single initial dose of 2 mg of aflibercept”, followed by *two* secondary doses of 2 mg of aflibercept,” before transitioning to tertiary doses.

260. A physician practicing the dosing regimen instructed by Eylea’s® label for the treatment of AMD would meet this limitation of claim 5, and physician administering YESAFILI™ in the same manner would also meet this limitation.

261. Further, the proposed labeling for YESAFILI™ instructs physicians to administer YESAFILI™ in exactly the same way as Eylea®. Specifically, the YESAFILI™ label instructs physicians to treat the angiogenic eye disorder of AMD by administering 2 mg of YESAFILI™ (aflibercept-jbvf) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”

262. Accordingly, the YESAFILI™ label instructs physicians to treat the angiogenic eye disorder AMD by administering a single “initial” dose of 2 mg aflibercept-jbvf, followed by a “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks later, followed by another “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks after that, followed by a tertiary dose of 2 mg YESAFILI™ (aflibercept-jbvf) eight weeks after that (*i.e.*, eight weeks after the second, “secondary” dose), followed by additional “tertiary” doses of 2 mg Eylea® at 8 week intervals thereafter.

263. In other words, when the YESAFILI™ label instructs a physician to administer 2 mg YESAFILI™ (aflibercept-jbvf) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months”, before switching to dosing once every 8 weeks, it expressly instructs physicians to administer “a single initial dose of 2 mg of aflibercept”, followed by *two* secondary doses of 2 mg of aflibercept,” before transitioning to tertiary doses.

264. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 3 *and* the further limitation of claim 5, “wherein only two secondary doses are administered to the patient.” Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 3 *and* the further limitation of claim 5, “wherein only two secondary doses are administered to the patient”, and specifically intends this infringing activity of claim 5

265. I also incorporate by reference my analysis of this claim 5 in the claim charts appended hereto as Appendix C as though set forth fully herein.

8. Claim 6

266. Claim 6 of the '572 patent recites:

6. The method of claim 3 wherein the aflibercept is formulated as an isotonic solution.

267. I understand that claim 6 depends from claim 3, which depends from claim 2, which depends from claim 1. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 3 of the '572 patent. I incorporate the analysis of claim 3 as though fully set forth herein.

268. In addition, Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 3 *and* the further limitation of claim 6, "wherein the afibercept is formulated as an isotonic solution."

269. I am informed that another of Regeneron's experts, Dr. Bernhardt L. Trout, has offered the opinion that YESAFILI™ is formulated as an isotonic solution." I have been informed that Dr. Trout has analyzed Mylan's formulation of YESAFILI™ (afibercept-jbvf) and concluded that YESAFILI™ (afibercept-jbvf) is formulated as an isotonic solution. I accept and adopt this conclusion and, on that basis, understand the performance of the method of claim 3 using YESAFILI™ to meet every limitation of claim 6.

270. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 3 using afibercept "wherein the afibercept is formulated as an isotonic solution," as claim 6 requires. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 3 using afibercept "wherein the afibercept is formulated as an isotonic solution", and specifically intends this infringing activity of claim 6.

271. I also incorporate by reference my analysis of claim 6 in the claim charts appended hereto as Appendix C as though set forth fully herein.

9. Claim 7

272. Claim 7 of the '572 patent recites:

7. The method of claim 3 wherein the afibercept is formulated with a nonionic surfactant.

273. I understand that claim 7 depends from claim 3, which depends from claim 2, which depends from claim 1. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan's

marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 3 of the '572 patent. I incorporate the analysis of claim 3 as though fully set forth herein.

274. Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 3 *and* the further limitation of claim 7, "wherein the aflibercept is formulated with a nonionic surfactant."

275. I am informed that another of Regeneron's experts, Dr. Bernhardt L. Trout, has offered the opinion that YESAFILI™ is formulated with a nonionic surfactant. I have been informed that Dr. Trout has analyzed Mylan's formulation of YESAFILI™ (aflibercept-jbvf) and concluded that YESAFILI™ (aflibercept-jbvf) is formulated with a nonionic surfactant. I accept and adopt this conclusion and, on that basis, understand the performance of the method of claim 3 using YESAFILI™ to meet every limitation of claim 7.

276. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 3 using aflibercept "wherein the aflibercept is formulated with a nonionic surfactant," as claim 7 requires. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 3 using aflibercept "wherein the aflibercept is formulated as with a nonionic surfactant", and specifically intends this infringing activity of claim 7.

277. I also incorporate by reference my analysis of claim 7 in the claim charts appended hereto as Appendix C as though set forth fully herein.

10. Claim 8

278. Claim 8 of the '572 patent recites:

8. The method of claim 2 wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

279. I understand that claim 8 depends from claim 2, which depends from claim 1. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 2 of the '572 patent. I incorporate that analysis of claim 2 as though fully set forth herein.

280. Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 2 *and* the further limitation of claim 8, "wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score."

281. As I explained above, Mylan reported the results of its Phase III clinical trial in patients with DME using YESAFILI™ to the FDA, as part of its BLA, and to doctors at conferences like AAO. *Supra* Section III.D.3(e). I incorporate that analysis as though set forth herein. That data demonstrates that when YESAFILI™ is administered according to the method of claim 1, patients gained more than 8 letters of BCVA according to ETDRS Letter Score within 52 weeks of the initial dose. In particular, Mylan's clinical study reported that doctors measured a gain of more than 10 letters in 57.4% of patients to whom they administered YESAFILI™ according to Mylan's study protocol.²³⁴ Furthermore, I have reviewed the individual patient efficacy results, and have identified several patients to whom doctors administered YESAFILI™ in accordance with the method of claim 1 and then measured a gain

²³⁴ MYL-AFL-BLA1056844 at -6950; MYL-AFL0089391 at -89399.

of more than 8 letters BCVA according to ETDRS within 52 weeks of the initial dose.²³⁵

Examples include patients 110003, 110012, 117013, 202003, and 203007.²³⁶

282. This data, which Mylan has presented both to the FDA as part of its BLA and to doctors at conferences,²³⁷ demonstrates that if Mylan markets YESAFILI™ according to its proposed labeling, doctors will in fact perform the method of claim 2, *and* measure a BCVA gain of at least 8 letters ETDRS letter score within 52 weeks of the initial dose, as claim 8 requires.

283. Mylan's phase III study was performed in patients with DME, but Mylan's proposed label for YESAFILI™ also instructs administration of YESAFILI™ to treat patients with AMD. As I described above, *supra* Section III.D.3, Mylan's proposed labeling instructs doctors to treat patients with AMD in a manner that practices the regimen recited in claim 1 of the '572 patent. Mylan's proposed labeling also instructs doctors to use YESAFILI™ in the same way they would use Eylea®, and that YESAFILI™ is clinically equivalent to Eylea® when used according to its label.²³⁸ I have treated AMD patients using Eylea® in my own clinical practice, using an initial dose of 2 mg Eylea®, two secondary doses of 2 mg Eylea® two weeks after the immediately preceding dose, and then tertiary doses of 2 mg Eylea® four weeks after the immediately preceding dose. I measure the BCVA of such patients before every injection, and I have measured BCVA gains of at least 8 letters according to ETDRS Letter Score in such patients within 52 weeks of their initial dose. On this basis, in combination with Mylan's instruction to doctors that YESAFILI™ is clinically equivalent to Eylea®, I conclude that if

²³⁵ *Supra* Section VI.D.e.1.ii..

²³⁶ *Supra* Section VI.D.e.1.ii..

²³⁷ MYL-AFL-BLA1056844 at -6950; MYL-AFL0089391 at -89399.

²³⁸ *Supra* section VI.D.2..

Mylan markets YESAFILI™ according to its proposed labeling, doctors will in fact perform the method of claim 2 to treat AMD, *and* perform the additional limitation of claim 8 by measuring a BCVA gain of at least 8 letters ETDRS within 52 weeks of their initial dose.

284. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 8, “wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.” Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 8, “wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score”, and specifically intends this infringing activity of claim 8.

285. I also incorporate by reference my analysis with respect to Claim 2 above with respect to BCVA, ETDRS, and the fact that such claims are not limited to clinical trials.²³⁹ That analysis applies equally to this claim. For the same reasons I explained with respect to claim 2, the POSA would not understand this claim to require measurement of a gain of 8 letters BCVA within 52 weeks of the initial dose using an ETDRS chart; the POSA would instead understand this claim to require measuring a gain in BCVA that is equivalent to 8 letters BCVA according ETDRS letter score, and would understand that such a gain can be measured by performing any appropriate visual acuity testing protocol (e.g., Snellen).²⁴⁰ Regardless, even were this claim interpreted to require measurement using an ETDRS chart, it is still my opinion that Mylan induces infringement of this claim for the same reasons I explained with respect to claim 2 above—namely, because physicians do in fact use ETDRS charts in clinical practice to measure

²³⁹ *Supra* Sections VI.D.4.a, VI.D.4 b, and VI.D.4c.

²⁴⁰ *Supra* Section VI.D.4.b.1.

visual acuity gain (I myself have done so), and physicians will use ETDRS charts to measure gains of 8 letters BCVA within 52 weeks of the initial dose according to EDTRS if Mylan markets YESAFILI™ according to its proposed labeling, just as Mylan's proposed labeling recommends, encourages, and promotes.²⁴¹ Furthermore, even were this claim interpreted to require use of an ETDRS chart, or an ETDRS protocol, to measure visual acuity, Mylan would induce infringement of this claim under the doctrine of equivalents, for all the reasons I explained above with respect to claim 2.²⁴² Again, for all the reasons I explained with respect to claim 2, this claim is not limited to the performance of its method in clinical trials, and the POSA would not understand the reference to ETDRS and BCVA to mean that the method of this claim can only be performed during clinical trials.²⁴³ In the event the Court interprets this claim to not require the physician to perform the step of measuring a gain in visual acuity, I likewise conclude that Mylan would induce infringement of this claim, because if Mylan markets YESAFILI™ in accordance with its approved labeling, at least one physician will perform the steps of claim 1 with respect to a patient who experiences a gain of at least 8 letters BCVA according to ETDRS letter score within 52 weeks of the initial dose, and Mylan's proposed labeling recommends, encourages and promotes this conduct.

286. I also incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix C as though set forth fully herein.

11. Claim 9

287. Claim 9 of the '572 patent recites:

²⁴¹ *Supra* Section VI.4.b.2.

²⁴² *Supra* Section VI.4.b.3.

²⁴³ *Supra* Section VI.D.4.d.

9. The method of claim 8 wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose.

288. I understand that claim 9 depends from claim 8, which depends from claim 2, which depends from claim 1. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 8 of the '572 patent. I incorporate the analysis of claim 8 as though fully set forth herein.

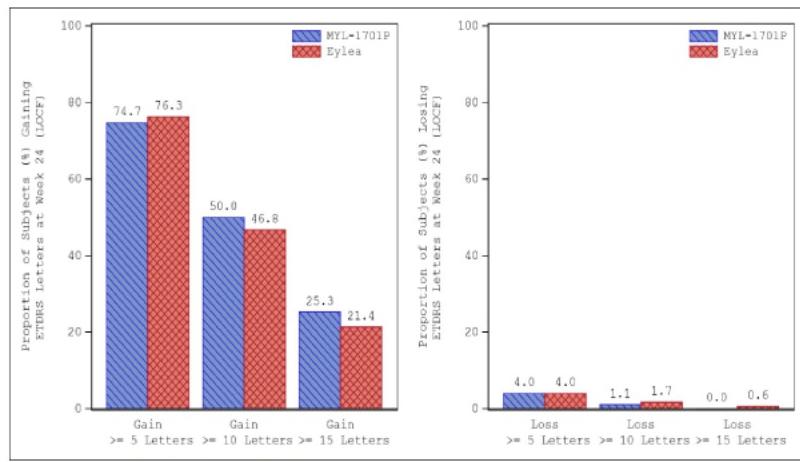
289. Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 8 *and* the further limitation of claim 9, "wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose."

290. Mylan also reported the week 24 results of its Phase III clinical in patients with DME using YESAFILI™ to the FDA, as part of its BLA.²⁴⁴ That data demonstrates that when YESAFILI™ is administered according to the method of claim 1, patients gained more than 7 letters of BCVA according to ETDRS Letter Score within 24 weeks of the initial dose. In particular, Mylan's clinical study reported that at 24 weeks, doctors measured a gain of more than 10 letters in 50.0% of patients to whom they administered YESAFILI™ according to Mylan's study protocol.²⁴⁵

²⁴⁴ MYL-AFL-BLA0552809.

²⁴⁵ MYL-AFL-BLA1056844 at -6950; MYL-AFL0089391 at -89399.

Figure 9: Proportion of Subjects Who Gained or Lost ≥5, ≥10 or ≥15 Letters, at Week 24



Source: Figure 14.2.2.4.1a; Listing 16.2.6.5a

291. Furthermore, I have reviewed the individual patient efficacy results, and have identified several patients to whom doctors administered YESAFILI™ in accordance with the method of claim 1 and then measured a gain of more than 8 letters BCVA according to ETDRS within 24 weeks of the initial dose.²⁴⁶ Examples include patients 110003, 110012, 117013, 202003, and 203007.²⁴⁷

292. This data, which Mylan has presented to the FDA as part of its BLA,²⁴⁸ demonstrates that if Mylan markets YESAFILI™ according to its proposed labeling, doctors will in fact perform the method of claim 8 to treat DME, *and* measure a BCVA gain of at least 8 letters ETDRS within 24 weeks of the initial dose.

293. Mylan's phase III study was performed in patients with DME, but Mylan's proposed label for YESAFILI™ also instructs administration of YESAFILI™ to treat patients

²⁴⁶ *Supra* Section VI.D.e.1.ii.

²⁴⁷ *Supra* Section VI.D.e.1.ii.

²⁴⁸ MYL-AFL-BLA1056844 at -6950; MYL-AFL0089391 at -89399.

with AMD. As I described above, *supra* Section VI.D.3, Mylan's proposed labeling instructs doctors to treat patients with AMD in a manner that practices the regimen recited in claim 1 of the '572 patent. Mylan's proposed labeling also instructs doctors to use YESAFILI™ in the same way they would use Eylea®, and that YESAFILI™ is clinically equivalent to Eylea® when used according to its label.²⁴⁹ I have treated AMD patients using Eylea® in my own clinical practice, using an initial dose of 2 mg Eylea®, two secondary doses of 2 mg Eylea® two weeks after the immediately preceding dose, and then tertiary doses of 2 mg Eylea® four weeks after the immediately preceding dose. I measure the BCVA of such patients before every injection, and I have measured BCVA gains of 8 letters according to ETDRS Letter Score in such patients within 24 weeks of the initial dose. On this basis, in combination with Mylan's instruction to doctors that YESAFILI™ is clinically equivalent to Eylea®, I conclude that if Mylan markets YESAFILI™ according to its proposed labeling, doctors will in fact perform the method of claim 3 to treat AMD, *and* measure a BCVA gain of at least 8 letters ETDRS within 24 weeks of the initial dose.

294. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 8 and the further limitation of claim 9, "wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose." Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 8 and the further limitation of claim 9, "wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose", and specifically intends this infringing activity of claim 9.

²⁴⁹ *Supra* section VI.D.2.

295. I also incorporate by reference my analysis with respect to Claim 2 above with respect to BCVA, ETDRS, and the fact that such claims are not limited to clinical trials.²⁵⁰ That analysis applies equally to this claim. For the same reasons I explained with respect to claim 2, the POSA would not understand this claim to require measurement of a gain of 8 letters BCVA within 24 weeks of the initial dose using an ETDRS chart; the POSA would instead understand this claim to require measuring a gain in BCVA that is equivalent to 8 letters BCVA according ETDRS letter score, and would understand that such a gain can be measured by performing any appropriate visual acuity testing protocol (e.g., Snellen).²⁵¹ Regardless, even were this claim interpreted to require measurement using an ETDRS chart, it is still my opinion that Mylan induces infringement of this claim for the same reasons I explained with respect to claim 2 above—namely, because physicians do in fact use ETDRS charts in clinical practice to measure visual acuity gain (I myself have done so), and physicians will use ETDRS charts to measure gains of 8 letters BCVA within 24 weeks of the initial dose according to EDTRS if Mylan markets YESAFILI™ according to its proposed labeling, just as Mylan’s proposed labeling recommends, encourages, and promotes.²⁵² Furthermore, even were this claim interpreted to require use of an ETDRS chart, or an ETDRS protocol, to measure visual acuity, Mylan would induce infringement of this claim under the doctrine of equivalents, for all the reasons I explained above with respect to claim 2.²⁵³ Again, for all the reasons I explained with respect to

²⁵⁰ *Supra* Sections VI.D.4.a, VI.D.4 b, and VI.D.4c.

²⁵¹ *Supra* Section VI.D.4.b.1.

²⁵² *Supra* Section VI.4.b.2.

²⁵³ *Supra* Section VI.4.b.3.

claim 2, this claim is not limited to the performance of its method in clinical trials, and the POSA would not understand the reference to ETDRS and BCVA to mean that the method of this claim can only be performed during clinical trials.²⁵⁴ In the event the Court interprets this claim to not require the physician to perform the step of measuring a gain in visual acuity, I likewise conclude that Mylan would induce infringement of this claim, because if Mylan markets YESAFILI™ in accordance with its approved labeling, at least one physician will perform the steps of claim 1 with respect to a patient who experiences a gain of at least 8 letters BCVA according to ETDRS letter score within 24 weeks of the initial dose, and Mylan's proposed labeling recommends, encourages and promotes this conduct.

296. I also incorporate by reference my analysis of claim 9 in the claim charts appended hereto as Appendix C as though set forth fully herein.

12. Claim 10

297. Claim 10 of the '572 patent recites:

10. The method of claim 2 wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

298. I understand that claim 10 depends from claim 2, which depends from claim 1. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 2 of the '572 patent. I incorporate the analysis of claim 2 as though fully set forth herein.

299. Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 2 *and* the further limitation of claim 10, "wherein the patient gains at least 9 letters Best

²⁵⁴ *Supra* Section VI.D.4.d.

Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.”

300. As I explained above, Mylan reported the results of its Phase III clinical trial in patients with DME using YESAFILI™ to the FDA, as part of its BLA, and to doctors at conferences like AAO. *Supra* Section III.D.3(e). I incorporate that analysis as though set forth herein. That data demonstrates that when YESAFILI™ is administered according to the method of claim 1, patients gained more than 9 letters of BCVA according to ETDRS Letter Score within 52 weeks of the initial dose. In particular, Mylan’s clinical study reported that doctors measured a gain of more than 10 letters in 57.4% of patients to whom they administered YESAFILI™ according to Mylan’s study protocol.²⁵⁵ Furthermore, I have reviewed the individual patient efficacy results, and have identified several patients to whom doctors administered YESAFILI™ in accordance with the method of claim 1 and then measured a gain of more than 9 letters BCVA according to ETDRS within 52 weeks of the initial dose.²⁵⁶ Examples include patients 110003, 110012, 117013, 202003, and 203007.²⁵⁷

301. This data, which Mylan has presented both to the FDA as part of its BLA and to doctors at conferences,²⁵⁸ demonstrates that if Mylan markets YESAFILI™ according to its proposed labeling, doctors will in fact perform the method of claim 2, *and* measure a BCVA gain of at least 9 letters ETDRS within 52 weeks of the initial dose

²⁵⁵ MYL-AFL-BLA1056844 at -6950; MYL-AFL0089391 at -89399.

²⁵⁶ *Supra* Section VI.D.e.1.ii.

²⁵⁷ *Supra* Section VI.D.e.1.ii.

²⁵⁸ MYL-AFL-BLA1056844 at -6950; MYL-AFL0089391 at -89399.

302. Mylan's phase III study was performed in patients with DME, but Mylan's proposed label for YESAFILI™ also instructs administration of YESAFILI™ to treat patients with AMD. As I described above, *supra* Section III.D.3, Mylan's proposed labeling instructs doctors to treat patients with AMD in a manner that practices the regimen recited in claim 1 of the '572 patent. Mylan's proposed labeling also instructs doctors to use YESAFILI™ in the same way they would use Eylea®, and that YESAFILI™ is clinically equivalent to Eylea® when used according to its label.²⁵⁹ I have treated AMD patients using Eylea® in my own clinical practice, using an initial dose of 2 mg Eylea®, two secondary doses of 2 mg Eylea® two weeks after the immediately preceding dose, and then tertiary doses of 2 mg Eylea® four weeks after the immediately preceding dose. I measure the BCVA of such patients before every injection, and I have measured BCVA gains of at least 9 letters according to ETDRS Letter Score in such patients within 52 weeks of the initial dose. On this basis, in combination with Mylan's instruction to doctors that YESAFILI™ is clinically equivalent to Eylea®, I conclude that if Mylan markets YESAFILI™ according to its proposed labeling, doctors will in fact perform the method of claim 2 to treat AMD, *and* measure BCVA gains of at least 9 letters according to ETDRS letter score within 52 weeks of the initial dose.

303. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 2 and the additional limitation of claim 10, "wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score." Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 2 and the additional limitation of claim 10, "wherein the patient gains at least 9 letters

²⁵⁹ *Supra* section VI.D.2.

Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score”, and specifically intends this infringing activity of claim 10.

304. I also incorporate by reference my analysis with respect to Claim 2 above with respect to BCVA, ETDRS, and the fact that such claims are not limited to clinical trials.²⁶⁰ That analysis applies equally to this claim. For the same reasons I explained with respect to claim 2, the POSA would not understand this claim to require measurement of a gain of 9 letters BCVA within 52 weeks of the initial dose using an ETDRS chart; the POSA would instead understand this claim to require measuring a gain in BCVA that is equivalent to 9 letters BCVA according ETDRS letter score, and would understand that such a gain can be measured by performing any appropriate visual acuity testing protocol (e.g., Snellen).²⁶¹ Regardless, even were this claim interpreted to require measurement using an ETDRS chart, it is still my opinion that Mylan induces infringement of this claim for the same reasons I explained with respect to claim 2 above—namely, because physicians do in fact use ETDRS charts in clinical practice to measure visual acuity gain (I myself have done so), and physicians will use ETDRS charts to measure gains of 9 letters BCVA within 52 weeks of the initial dose according to EDTRS if Mylan markets YESAFILI™ according to its proposed labeling, just as Mylan’s proposed labeling recommends, encourages, and promotes.²⁶² Furthermore, even were this claim interpreted to require use of an ETDRS chart, or an ETDRS protocol, to measure visual acuity, Mylan would induce infringement of this claim under the doctrine of equivalents, for all the reasons I

²⁶⁰ *Supra* Sections VI.D.4.a, VI.D.4 b, and VI.D.4c.

²⁶¹ *Supra* Section VI.D.4.b.1.

²⁶² *Supra* Section VI.4.b.2.

explained above with respect to claim 2.²⁶³ Again, for all the reasons I explained with respect to claim 2, this claim is not limited to the performance of its method in clinical trials, and the POSA would not understand the reference to ETDRS and BCVA to mean that the method of this claim can only be performed during clinical trials.²⁶⁴ In the event the Court interprets this claim to not require the physician to perform the step of measuring a gain in visual acuity, I likewise conclude that Mylan would induce infringement of this claim, because if Mylan markets YESAFILI™ in accordance with its approved labeling, at least one physician will perform the steps of claim 1 with respect to a patient who experiences a gain of at least 9 letters BCVA according to ETDRS letter score within 52 weeks of the initial dose, and Mylan's proposed labeling recommends, encourages and promotes this conduct.

305. I also incorporate by reference my analysis of claim 10 in the claim charts appended hereto as Appendix C as though set forth fully herein.

13. Claim 11

306. Claim 11 of the '572 patent recites:

5. The method of claim 10 wherein only two secondary doses are administered to the patient.

307. I understand that claim 11 depends from claim 10, which depends from claim 2, which depends from claim 1. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of

²⁶³ *Supra* Section VI.4.b.3.

²⁶⁴ *Supra* Section VI.D.4.d.

claim 10 of the '572 patent. I incorporate the analysis of claim 10 as though fully set forth herein.

308. Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 10 *and* the further limitation of claim 11, "wherein only two secondary doses are administered to the patient."

309. It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to treat AMD by administering an "initial" dose of 2 mg Eylea® (aflibercept), followed by two "secondary" doses of 2 mg Eylea® (aflibercept), followed by one or more "tertiary" doses of 2 mg Eylea® (aflibercept).

310. Specifically, the Eylea® label instructs physicians to treat the angiogenic eye disorder of AMD by administering 2 mg of Eylea® (aflibercept) "by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)." ²⁶⁵

311. Accordingly, the Eylea® label instructs physicians to treat the angiogenic eye disorder AMD by administering a single "initial" dose of 2 mg aflibercept, followed by a "secondary" dose of 2 mg Eylea® (aflibercept) four weeks later, followed by another "secondary" dose of 2 mg Eylea® (aflibercept) four weeks after that, followed by a tertiary dose of 2 mg Eylea® (aflibercept) eight weeks after that (*i.e.*, eight weeks after the second, "secondary" dose), followed by additional "tertiary" doses of 2 mg Eylea® at 8 week intervals thereafter.

312. In other words, when the Eylea® label instructs a physician to administer 2 mg Eylea® (aflibercept) "by intravitreal injection every 4 weeks (approximately every 28 days,

²⁶⁵ Eylea® Label (2022) at 1-2.

monthly) for the first three months”, before switching to dosing once every 8 weeks, it expressly instructs physicians to administer “a single initial dose of 2 mg of aflibercept”, followed by *two* secondary doses of 2 mg of aflibercept,” before transitioning to tertiary doses.²⁶⁶

313. A physician practicing the dosing regimen instructed by Eylea® label for the treatment of AMD would meet this limitation of claim 11, and physician administering YESAFILI™ in the same manner would also meet this limitation.

314. Further, the proposed labeling for YESAFILI™ instructs physicians to administer YESAFILI™ in exactly the same way as Eylea®. Specifically, the YESAFILI™ label instructs physicians to treat the angiogenic eye disorder of AMD by administering 2 mg of YESAFILI™ (aflibercept-jbvf) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”²⁶⁷

315. Accordingly, the YESAFILI™ label instructs physicians to treat the angiogenic eye disorder AMD by administering a single “initial” dose of 2 mg aflibercept-jbvf, followed by a “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks later, followed by another “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks after that, followed by a tertiary dose of 2 mg YESAFILI™ (aflibercept-jbvf) eight weeks after that (*i.e.*, eight weeks after the second, “secondary” dose), followed by additional “tertiary” doses of 2 mg Eylea® at 8 week intervals thereafter.

316. In other words, when the YESAFILI™ label instructs a physician to administer 2 mg YESAFILI™ (aflibercept-jbvf) “by intravitreal injection every 4 weeks (approximately every

²⁶⁶ Eylea® Label (2022) at 1-2.

²⁶⁷ MYL-AFL-BLA1079688 at -1079688 to -1079689.

28 days, monthly) for the first three months”, before switching to dosing once every 8 weeks, it expressly instructs physicians to administer “a single initial dose of 2 mg of aflibercept”, followed by *two* secondary doses of 2 mg of aflibercept,” before transitioning to tertiary doses.²⁶⁸

317. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 10 *and* the further limitation of claim 11, “wherein only two secondary doses are administered to the patient.” Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 10 *and* the further limitation of claim 11, “wherein only two secondary doses are administered to the patient”, and specifically intends this infringing activity of claim 11.

318. I also incorporate by reference my analysis of claim 11 in the claim charts appended hereto as Appendix C as though set forth fully herein.

14. Claim 12

319. Claim 12 of the ’572 patent recites:

12. The method of claim 10 wherein the aflibercept is formulated as an isotonic solution.

320. I understand that claim 12 depends from claim 10, which depends from claim 2, which depends from claim 1. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan’s marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 10 of the ’572 patent. I incorporate the analysis of claim 10 as though fully set forth herein.

²⁶⁸ MYL-AFL-BLA1079688 at -1079688 to -1079689.

321. Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 10 *and* the further limitation of claim 12, "wherein the aflibercept is formulated as an isotonic solution."

322. I am informed that another of Regeneron's experts, Dr. Bernhardt L. Trout, has offered the opinion that YESAFILI™ is formulated as an isotonic solution." I have been informed that Dr. Trout has analyzed Mylan's formulation of YESAFILI™ (aflibercept-jbvf) and concluded that YESAFILI™ (aflibercept-jbvf) is formulated as an isotonic solution. I accept and adopt this conclusion and, on that basis, understand the performance of the method of claim 3 using YESAFILI™ to meet every limitation of claim 12.

323. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 10 using aflibercept "wherein the aflibercept is formulated as an isotonic solution," as claim 12 requires. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 10 and using aflibercept "wherein the aflibercept is formulated as an isotonic solution", and specifically intends this infringing activity of claim 12.

324. I also incorporate by reference my analysis of claim 12 in the claim charts appended hereto as Appendix C as though set forth fully herein.

15. Claim 13

325. Claim 13 of the '572 patent recites:

13. The method of claim 10 wherein the aflibercept is formulated with a nonionic surfactant.

326. I understand that claim 13 depends from claim 10, which depends from claim 2, which depends from claim 1. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan's

marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 10 of the '572 patent. I incorporate that analysis as though fully set forth herein.

327. Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 10 *and* the further limitation of claim 13, "wherein the afibbercept is formulated with a nonionic surfactant."

328. I am informed that another of Regeneron's experts, Dr. Bernhardt L. Trout, has offered the opinion that YESAFILI™ is formulated with a nonionic surfactant. I have been informed that Dr. Trout has analyzed Mylan's formulation of YESAFILI™ (afibbercept-jbvf) and concluded that YESAFILI™ (afibbercept-jbvf) is formulated with a nonionic surfactant. I accept and adopt this conclusion and, on that basis, understand the performance of the method of claim 3 using YESAFILI™ to meet every limitation of claim 13.

329. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 10 using afibbercept "wherein the afibbercept is formulated with a nonionic surfactant," as claim 13 requires. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 10 using afibbercept "wherein the afibbercept is formulated as with a nonionic surfactant", and specifically intends this infringing activity of claim 13.

330. I also incorporate by reference my analysis of claim 13 in the claim charts appended hereto as Appendix C as though set forth fully herein.

16. Claim 14

331. Claim 14 of the '572 patent recites:

14. The method of claim 1 wherein exclusion criteria for the patient include both of:
 - (1) active ocular inflammation; and
 - (2) active ocular or periocular infection

a) Mylan Induces Infringement of Claim 14

332. The POSA would understand the method of claim 14 to require that a doctor perform a method of treating an angiogenic eye disorder in a patient in need thereof comprising:

- (14a) Assessing the patient for active ocular inflammation
- (14b) Assessing the patient for active ocular or periocular infection
- (14c) If the assessment determines the patient does not have active ocular inflammation, active ocular or periocular infection:
 - (1a) sequentially administering to the patient by intravitreal injection a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;
 - (1b) wherein each secondary dose is administered approximately 4 weeks following the immediately preceding dose; and
 - (1c) wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose;
 - (1d) wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose.

333. I understand that claim 14 depends from claim 1. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As I described above in Section III.D.3, if Mylan markets YESAFILI™ in accordance with its proposed label, physicians will perform a method of treating an angiogenic eye disorder in a patient in need thereof comprising each of steps (1a) through (1d) of claim 1. I incorporate the analysis of claim 1 as though set forth herein.

334. In addition, if Mylan markets YESAFILI™ in accordance with its proposed label, physicians will perform the method of *first* assessing the patient for active ocular inflammation, *then* assessing the patient for active ocular or periocular infection, and *then, if the assessment determines the patient does not have active ocular inflammation and does not have active ocular or periocular infection*, performing steps (1a) through (1d) of claim 1.

335. It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to assess patients for active ocular inflammation and active ocular or periocular infection, and then, on the basis of that assessment, administer Eylea® in accordance with steps (1a) through (1d).²⁶⁹

336. Specifically, the Eylea® label lists both “ocular or periocular infection” and “active intraocular inflammation” as contraindications for administration of Eylea®. As the POSA would understand, when a drug label lists conditions under the heading “Contraindications,” that label instructs physicians to assess patients for the presence of the contraindicated condition and to decline to treat patients with the drug that is the subject of the label if that assessment reveals the presence of the contraindicated condition. Accordingly, the Eylea® label instructs physicians to assess patients for active intraocular inflammation and active ocular or periocular infection before administering Eylea. A physician administering YESAFILI™ in the same manner would meet this limitation.²⁷⁰

337. Further, Mylan’s proposed YESAFILI™ labeling instructs physicians to assess and adhere to the same contraindications as Eylea’s® label.²⁷¹ Specifically, the YESAFILI™

²⁶⁹ Eylea® Label (2022) at 4.

²⁷⁰ Eylea® Label (2022) at 4.

²⁷¹ MYL-AFL-BLA1079688 at Highlights of Prescribing Information (listing as contraindications “Ocular or periocular infection” and “Active intraocular inflammation”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.1 (“YESAFILI is contraindicated in

label lists both “ocular or periocular infection” and “active intraocular inflammation” as contraindications for administration of YESAFILI™.

338. Accordingly, the YESAFILI™ label instructs physicians to assess patients for active intraocular inflammation and active ocular or periocular infection before administering YESAFILI. In this manner, the YESAFILI™ labeling expressly directs physicians to perform the method of claim 14.

339. Thus, by marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 14, “wherein exclusion criteria for the patient include both of: (1) active ocular inflammation; and (2) active ocular or periocular infection.” Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 1 and the additional step of claim 144, “wherein exclusion criteria for the patient include both of: (1) active ocular inflammation; and (2) active ocular or periocular infection”, and specifically intends this infringing activity of claim 14.

340. I also incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix C as though set forth fully herein.

b) Exclusion Criteria Do Not Suggest Claim 14 is Restricted To Clinical Trials

341. I am informed by counsel that Mylan asserts that the method of Claim 14 cannot be performed outside the clinical trial context, because claim 14 references “exclusion criteria.” That is not how the POSA would understand claim 14. “Exclusion criteria” are a concept that physicians apply in clinical practice, not just in the clinical trial context. Physicians are aware—and drug labels instruct—that certain drugs should not be given to patients with certain

patients with ocular or periocular infections.”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.2 (“YESAFILI is contraindicated in patients with active intraocular inflammation.”).

characteristics . In other words, therapy in such patients is contraindicated, and those patients are therefore excluded from therapy using the drug . The POSA reading claim 14 would understand the term “exclusion criteria” in precisely this way—*i.e.*, an instruction to look for the conditions that are contraindicated, and exclude any patients who possess those characteristics from drug therapy. Indeed, the whole specification of the Yancopoulos patents is consistent with this understanding, as it consistently refers to FDA approval of aflibercept to treat patients—*i.e.*, in regular practice, not in clinical trials.²⁷² Instead, when the Yancopoulos patents wish to refer to patients in the clinical trial setting, they refer to “human subjects.”²⁷³

17. Claim 15

342. Claim 15 of the '572 patent recites:

15. A method of treating diabetic macular edema in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept; wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose.

343. Claim 15 contains 4 limitations, each of which I address in turn below:

- (15pre) 15. A method of treating diabetic macular edema in a patient in need thereof comprising
- (15a) sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;

²⁷² See, e.g., '572 Patent, 2:61-63 (“Aflibercept (EYLEATM, Regeneron Pharmaceuticals, Inc) was approved by the FDA in November 2011, for the treatment of patients[.]”).

²⁷³ See, e.g. '572 Patent, claims 26 and 29 (requiring, e.g., doctors to measure a gain in patients in clinical practice at least as high as that measured in subjects in the ranibizumab clinical trial).

- (15b) wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and
- (15c) wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose.

344. By marketing YESAFILI™ in accordance with its proposed labeling, Mylan knows and specifically intends that physicians will perform every limitation of the method of claim 15. I explain the basis for my opinion in further detail below, and in the claim charts appended to this report at Appendix C. I hereby incorporate by reference my analysis in those claim charts as though set forth fully herein.

c) (15pre) A method of treating diabetic macular edema in a patient in need thereof comprising

345. With respect to the first limitation (also called the preamble)—“A method of treating diabetic macular edema in a patient in need thereof comprising”—it is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to administer Eylea® to patients in need of treatment for DME, in order to treat DME.²⁷⁴ Specifically, the Eylea® label instructs physicians to administer aflibercept to treat “Diabetic Macular Edema (DME).”²⁷⁵ A physician administering YESAFILI™ in the same manner would meet this limitation.

346. Further, Mylan’s proposed YESAFILI™ labeling instructs physicians to administer YESAFILI™ to patients in the same way and for the same reasons that physicians would administer Eylea®—including by administering YESAFILI™ to patients in need of

²⁷⁴ Eylea® Label (2022) at 1-2.

²⁷⁵ Eylea® Label (2022) at 1-2.

treatment for DME, in order to treat DME.²⁷⁶ Specifically, Mylan’s proposed labeling for YESAFILI™ expressly instructs physicians to administer YESAFILI™ to treat “Diabetic Macular Edema (DME).”²⁷⁷

347. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to administer YESAFILI™ to patients in need of treatment for DME, in order to treat DME. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will administer YESAFILI™ to treat DME in a manner consistent with Claim 15 of the ’572 Patent, and specifically intends this infringing activity of this limitation of claim 15.

348. I also incorporate by reference my analysis of this limitation of claim 15 in the claim charts appended hereto as Appendix C as though set forth fully herein.

- d) **(15a) sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept**

349. Limitation 15a requires that the physician “sequentially administer to the patient by intravitreal injection a single initial dose of 2 mg of aflibercept” followed by one or more “secondary” doses of 2 mg of aflibercept, followed by one or more “tertiary” doses of 2 mg of aflibercept. It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to administer Eylea® in order to treat DME, by administering an “initial” dose of 2 mg Eylea® (aflibercept), followed by one or more “secondary” doses of 2 mg Eylea® (aflibercept), followed by one or more “tertiary” doses of 2 mg Eylea® (aflibercept).

²⁷⁶ MYL-AFL-BLA1079688 at -1079688 to -1079689.

²⁷⁷ MYL-AFL-BLA1079688 at -1079688 to -1079689.

350. Specifically, the Eylea® label instructs physicians to treat the angiogenic eye disorder of DME by administering 2 mg of Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”²⁷⁸

351. Accordingly, the Eylea® label instructs physicians to treat the angiogenic eye disorder DME by administering a single “initial” dose of 2 mg aflibercept, followed by a “secondary” dose of 2 mg Eylea® (aflibercept) four weeks later, followed by another “secondary” dose of 2 mg Eylea® (aflibercept) four weeks after that, followed by a third “secondary” dose of 2 mg Eylea® (aflibercept) four weeks after that, followed by a fourth “secondary” dose of 2 mg Eylea® (aflibercept) four weeks after that, followed by a “tertiary” dose of 2 mg Eylea® (aflibercept) eight weeks after that (*i.e.*, eight weeks after the fourth, “secondary” dose), followed by additional “tertiary” doses of 2 mg Eylea® at 8 week intervals thereafter.

352. In other words, when the Eylea® label instructs a physician to administer 2 mg Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections”, it expressly instructs physicians to administer “a single initial dose of 2 mg of aflibercept, followed by [four] secondary doses of 2 mg of aflibercept.”²⁷⁹ When the Eylea® label instructs a physician that the first five injections should be “followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months),” the Eylea® label

²⁷⁸ Eylea® Label (2022) at 1-2.

²⁷⁹ Eylea® Label (2022) at 1-2.

expressly instructs physicians to administer “one or more tertiary doses of 2 mg of aflibercept.”²⁸⁰

353. A physician practicing the dosing regimen instructed by Eylea’s® label for the treatment of DME would meet this limitation of claim 15, and physician administering YESAFILI™ in the same manner would also meet this limitation.

354. Further, Mylan’s proposed YESAFILI™ labeling instructs physicians to administer YESAFILI™ to treat DME using precisely the same regimens as contained in Eylea’s® label.²⁸¹

355. Specifically, Mylan’s proposed YESAFILI™ labeling instructs physicians to treat the angiogenic eye disorder of DME by administering 2 mg of YESAFILI™ (aflibercept-jbvf) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”²⁸²

356. Accordingly, the YESAFILI™ label instructs physicians to treat the angiogenic eye disorder DME by administering a single “initial” dose of 2 mg aflibercept, followed by a “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks later, followed by another “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks after that, followed by a third “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks after that, followed by a fourth “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks after that, followed by a “tertiary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) eight weeks after that (*i.e.*,

²⁸⁰ Eylea® Label (2022) at 1-2.

²⁸¹ MYL-AFL-BLA1079688 at -1079688 to -1079689.

²⁸² MYL-AFL-BLA1079688 at -1079688 to -1079689.

eight weeks after the fourth, “secondary” dose), followed by additional “tertiary” doses of 2 mg YESAFILI™ at 8 week intervals thereafter.

357. In other words, when the YESAFILI™ label instructs a physician to administer 2 mg YESAFILI™ (aflibercept-jbvf) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections”, it expressly instructs physicians to sequentially administer “a single initial dose of 2 mg of aflibercept, followed by [four] secondary doses of 2 mg of aflibercept.”²⁸³ When the YESAFILI™ label instructs a physician that the first five injections should be “followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months),” the YESAFILI™ label expressly instructs physicians to sequentially administer “one or more tertiary doses of 2 mg of aflibercept.”²⁸⁴

358. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to “sequentially administer[] to the patient by intravitreal injection a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept” in order to treat DME. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will “sequentially administer[] to the patient by intravitreal injection a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept” in a manner consistent with Claim 15 of the ’572 Patent, and specifically intends this infringing activity of this limitation of claim 15.

359. I also incorporate by reference my analysis of this limitation of claim 15 in the claim charts appended hereto as Appendix C as though set forth fully herein.

²⁸³ MYL-AFL-BLA1079688 at -1079688 to -1079689.

²⁸⁴ MYL-AFL-BLA1079688 at -1079688 to -1079689.

- e) (15b) wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and

360. Limitation (15b) requires that the physician administer the doses described in limitation (15a), “wherein each secondary dose is administered approximately four weeks following the immediately preceding dose.” It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to administer an “initial” dose of 2 mg Eylea® (aflibercept), followed by four “secondary” doses of 2 mg Eylea® (aflibercept) “approximately four weeks following the immediately preceding dose,” in order to treat DME.²⁸⁵

361. Specifically, the Eylea® label instructs physicians to treat the angiogenic eye disorder of DME by administering 2 mg of Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”²⁸⁶ As I described above in connection with limitation (15a)—an analysis I incorporate herein by reference—this instruction directs physicians to administer one initial dose of 2 mg Eylea, followed by a first “secondary” dose of 2 mg Eylea four weeks later, followed by a second “secondary” dose of 2 mg Eylea four weeks after that, followed by a third “secondary” dose of 2 mg Eylea four weeks after that, followed by a fourth “secondary” dose of 2 mg Eylea four weeks after that, before transitioning to the administration of tertiary doses. Thus, the Eylea label expressly instructs physicians to administer an initial dose of 2 mg Eylea, followed by four secondary doses “wherein each secondary dose is administered approximately four weeks following the immediately preceding dose.” A physician administering YESAFILI™ in the same manner would meet this limitation.

²⁸⁵ Eylea® Label (2022) at 1-2.

²⁸⁶ Eylea® Label at 1-2.

362. A physician practicing the dosing regimen instructed by Eylea's® label for the treatment of DME would meet this limitation of claim 15, and physician administering YESAFILI™ in the same manner would also meet this limitation.

363. Further, the YESAFILI™ label instructs physicians to treat DME by administering 2 mg of YESAFILI™ (aflibercept-jbvf) "by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)."²⁸⁷ As I described above in connection with limitation (1a)—an analysis I incorporate herein by reference—this instruction directs physicians to administer one initial dose of 2 mg YESAFILI, followed by a first "secondary" dose of 2 mg YESAFILI™ four weeks later, followed by a second "secondary" dose of 2 mg Eylea® four weeks after that, followed by a third "secondary" dose of 2 mg YESAFILI™ four weeks after that, before transitioning to the administration of tertiary doses. Thus, the YESAFILI™ label expressly instructs physicians to administer an initial dose of 2 mg YESAFILI™, followed by four secondary doses "wherein each secondary dose is administered approximately four weeks following the immediately preceding dose," in order to treat DME.²⁸⁸

364. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to administer an initial dose of 2 mg YESAFILI™, followed by secondary doses, "wherein each secondary dose is administered approximately four weeks following the immediately preceding dose." Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will administer an initial dose of 2 mg YESAFILI™, followed by

²⁸⁷ MYL-AFL-BLA1079688 at -1079688 to -1079689.

²⁸⁸ MYL-AFL-BLA1079688 at -1079688 to -1079689.

secondary doses, “wherein each secondary dose is administered approximately four weeks following the immediately preceding dose,” in a manner consistent with Claim 15 of the ’572 Patent, and specifically intends this infringing activity of this limitation of claim 15.

365. I also incorporate by reference my analysis of this limitation of claim 15 charts appended hereto as Appendix C as though set forth fully herein.

f) (15c) wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose

227. Limitation (15c) requires that the physician administer the doses described in limitation (15a), “wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose.” It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to administer an “initial” dose of 2 mg Eylea® (aflibercept), followed by four “secondary” doses of 2 mg Eylea®, followed by one or more tertiary doses that are “administered approximately 8 weeks following the immediately preceding dose,” in order to treat DME.

228. Specifically, the Eylea® label instructs physicians to treat the angiogenic eye disorder of DME by administering 2 mg of Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”²⁸⁹ As I described above in connection with limitation (1a)—an analysis I incorporate herein by reference—this instruction directs physicians to administer one initial dose of 2 mg Eylea®, followed by a first “secondary” dose of 2 mg Eylea® four weeks later, followed by a second “secondary” dose of 2 mg Eylea® four weeks after that, followed by a third “secondary” dose of 2 mg Eylea® four weeks after

²⁸⁹ Eylea® Label (2022) at 1-2.

that, followed by a fourth “secondary” dose of 2 mg Eylea® four weeks after that, followed by a “tertiary” dose of 2 mg Eylea® (aflibercept) eight weeks after that (*i.e.*, eight weeks after the second, “secondary” dose), followed by additional “tertiary” doses of 2 mg Eylea® at 8 week intervals thereafter. Thus, the Eylea® label expressly instructs physicians to administer one or more tertiary doses “wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose.” A physician administering YESAFILI™ in the same manner would meet this limitation.

229. Thus, a physician practicing the dosing regimen instructed by Eylea’s® label for the treatment of DME would meet this limitation of claim 1, and a physician administering YESAFILI™ in the same manner would also meet this limitation.

230. Further, the YESAFILI™ label instructs physicians to treat the angiogenic eye disorder of DME by administering 2 mg of YESAFILI™ (aflibercept-jbv) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”²⁹⁰ As I described above in connection with limitation (1a)—an analysis I incorporate herein by reference—this instruction directs physicians to administer one initial dose of 2 mg YESAFILI, followed by a first “secondary” dose of 2 mg YESAFILI™ four weeks later, followed by a second “secondary” dose of 2 mg YESAFILI™ four weeks after that, followed by a third “secondary” dose of 2 mg YESAFILI four weeks after that, followed by a fourth “secondary” dose of 2 mg YESAFILI™ four weeks after that, followed by a “tertiary” dose of 2 mg YESAFILI (aflibercept-jbv) eight weeks after that (*i.e.*, eight weeks after the second, “secondary” dose), followed by additional “tertiary” doses of 2 mg YESAFILI™ at 8 week

²⁹⁰ MYL-AFL-BLA1079688 at -1079688 to -1079689.

intervals thereafter. Thus, the YESAFILI™ label expressly instructs physicians to administer one or more tertiary doses “wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose,” in order to treat DME.²⁹¹

231. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to administer one or more tertiary doses “wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose.” Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will administer one or more tertiary doses “wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose,” in a manner consistent with Claim 15 of the ’572 Patent, and specifically intends this infringing activity of this limitation of claim 15.

232. I also incorporate by reference my analysis of this limitation of claim 15 charts appended hereto as Appendix C as though set forth fully herein.

18. Claim 16

233. Claim 16 of the ’572 patent recites:

16. The method of claim 15 wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose.

234. I understand that claim 16 depends from claim 15. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan’s marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 15 of the ’572 patent. I incorporate the analysis of claim 15 as though fully set forth herein.

²⁹¹ MYL-AFL-BLA1079688 at -1079688 to -1079689.

235. In addition, Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 15 *and* the further limitation of claim 16, "wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose."

236. The POSA would understand Claim 16 to require a physician to perform the method of claim 15, and then perform the active step of measuring a gain in the patient's visual acuity within 52 weeks following the initial dose. As I explained above about gains in visual acuity for patients treated for DME in the context of limitation (1d), if Mylan markets YESAFILI™ in accordance with its proposed labeling, physicians who have administered YESAFILI™ in order to treat DME according to the proposed labeling for YESAFILI™ (*i.e.*, physicians who have performed the method of claim 15),²⁹² will then perform the additional step of measuring a gain in visual acuity within 52 weeks of the initial dose.²⁹³ I incorporate my analysis of Section (1d) by reference as though set forth herein, as that analysis applies equally to this claim. In the event the Court interprets this claim to not require the physician to perform the step of measuring a gain in visual acuity, I likewise conclude that Mylan would induce infringement of this claim, because if Mylan markets YESAFILI™ in accordance with its approved labeling, at least one physician will perform the steps of claim 1 with respect to a patient who experiences a gain in BCVA according to ETDRS letter score within 52 weeks of the initial dose, and Mylan's proposed labeling recommends, encourages and promotes this conduct.

237. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 15 and the additional limitation of claim 16,

²⁹² See *supra* Section VI.D.18.

²⁹³ *Supra* Section VI.D.3.e.

“wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose.”

Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 15 and the additional limitation of claim 16, “wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose”, and specifically intends this infringing activity of claim 16.

238. Finally, in the event the Court interprets this claim to not require the physician to perform the step of measuring a gain in visual acuity, I likewise conclude that Mylan would induce infringement of this claim, because if Mylan markets YESAFILI™ in accordance with its approved labeling, at least one physician will perform the steps of claim 15 with respect to a patient who experiences a gain in BCVA according to ETDRS letter score within 52 weeks of the initial dose, and Mylan’s proposed labeling recommends, encourages and promotes this conduct.

239. I also incorporate by reference my analysis of claim 16 in the claim charts appended hereto as Appendix C as though set forth fully herein.

19. Claim 17

240. Claim 17 of the ’572 patent recites:

17. The method of claim 16 wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

241. I understand that claim 17 depends from claim 16, which depends from claim 15. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan’s marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 16 of the ’572 patent. I incorporate the analysis of claim 16 as though fully set forth herein.

242. In addition, Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 16 *and* the further limitation of claim 17, "wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score."

243. Claim 17 requires a physician to perform the method of claim 16, and then measure a gain in the patient's visual acuity of at least 9 letters according to ETDRS Letter Score within 52 weeks following the initial dose. As I explained above, if Mylan markets YESAFILI™ in accordance with its proposed labeling, physicians who have administered YESAFILI™ in order to treat DME according to the proposed labeling for YESAFILI™ (*i.e.*, physicians who have performed the method of claim 15),²⁹⁴ will then perform the additional step of measuring a gain in visual acuity of at least 9 letters according to ETDRS letter score within 52 weeks of the initial dose.²⁹⁵

244. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 16 and the further limitation of claim 17, "wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score." Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 16 and perform the further limitation of claim 17, "wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score", and specifically intends this infringing activity of claim 17.

²⁹⁴ *Supra* Section VI.D.18.

²⁹⁵ *Supra* Section VI.D.12.

245. I also incorporate by reference my analysis with respect to Claim 2 above with respect to BCVA, ETDRS, and the fact that such claims are not limited to clinical trials.²⁹⁶ That analysis applies equally to this claim. For the same reasons I explained with respect to claim 2, the POSA would not understand this claim to require measurement of a gain of 9 letters BCVA within 52 weeks of the initial dose using an ETDRS chart; the POSA would instead understand this claim to require measuring a gain in BCVA that is equivalent to 9 letters BCVA according ETDRS letter score, and would understand that such a gain can be measured by performing any appropriate visual acuity testing protocol (e.g., Snellen).²⁹⁷ Regardless, even were this claim interpreted to require measurement using an ETDRS chart, it is still my opinion that Mylan induces infringement of this claim for the same reasons I explained with respect to claim 2 above—namely, because physicians do in fact use ETDRS charts in clinical practice to measure visual acuity gain (I myself have done so), and physicians will use ETDRS charts to measure gains of 9 letters BCVA within 52 weeks of the initial dose according to EDTRS if Mylan markets YESAFILI™ according to its proposed labeling, just as Mylan’s proposed labeling recommends, encourages, and promotes.²⁹⁸ Furthermore, even were this claim interpreted to require use of an ETDRS chart, or an ETDRS protocol, to measure visual acuity, Mylan would induce infringement of this claim under the doctrine of equivalents, for all the reasons I explained above with respect to claim 2.²⁹⁹ Again, for all the reasons I explained with respect to

²⁹⁶ *Supra* Sections VI.D.4.a, VI.D.4 b, and VI.D.4c.

²⁹⁷ *Supra* Section VI.D.4.b.1.

²⁹⁸ *Supra* Section VI.4.b.2.

²⁹⁹ *Supra* Section VI.4.b.3.

claim 2, this claim is not limited to the performance of its method in clinical trials, and the POSA would not understand the reference to ETDRS and BCVA to mean that the method of this claim can only be performed during clinical trials.³⁰⁰ Finally, in the event the Court interprets this claim to not require the physician to perform the step of measuring a gain in visual acuity, I likewise conclude that Mylan would induce infringement of this claim, because if Mylan markets YESAFILI™ in accordance with its approved labeling, at least one physician will perform the steps of claim 15 with respect to a patient who experiences a gain of at least 9 letters BCVA within 52 weeks of the initial dose, as claim 17 requires, and Mylan's proposed labeling recommends, encourages and promotes this conduct.

246. I also incorporate by reference my analysis of claim 17 in the claim charts appended hereto as Appendix C as though set forth fully herein.

20. Claim 18

247. Claim 18 of the '572 patent recites:

18. The method of claim 17 wherein the aflibercept is formulated as an isotonic solution.

248. I understand that claim 18 depends from claim 17, which depends from claim 16, which depends from claim 15. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 17 of the '572 patent. I incorporate that analysis as though fully set forth herein.

249. In addition, Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 17, "wherein the aflibercept is formulated as an isotonic solution."

³⁰⁰ *Supra* Section VI.D.4.d.

250. I am informed that another of Regeneron's experts, Dr. Bernhardt L. Trout, has offered the opinion that YESAFILI™ is formulated as an isotonic solution." I have been informed that Dr. Trout has analyzed Mylan's formulation of YESAFILI™ (aflibercept-jbvf) and concluded that YESAFILI™ (aflibercept-jbvf) is formulated as an isotonic solution. I accept and adopt this conclusion and, on that basis, understand the performance of the method of claim 3 using YESAFILI™ to meet every limitation of claim 18.

251. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 17 using aflibercept "wherein the aflibercept is formulated as an isotonic solution," as claim 18 requires. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 3 using aflibercept "wherein the aflibercept is formulated as an isotonic solution", and specifically intends this infringing activity of claim 18.

252. I also incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix C as though set forth fully herein.

21. Claim 19

253. Claim 19 of the '572 patent recites:

19. The method of claim 17 wherein the aflibercept is formulated with a non-ionic surfactant.

254. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 17 of the '572 patent. I incorporate that analysis as though fully set forth herein.

255. In addition, Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 17 and the additional limitation of claim 19, "wherein the aflibercept is formulated with a nonionic surfactant."

256. I also incorporate by reference my analysis of claim 19 in the claim charts appended hereto as Appendix C as though set forth fully herein.

22. Claim 20

257. Claim 20 of the '572 patent recites:

20. The method of claim 17 wherein the patient achieves a gain in visual acuity within 24 weeks following the initial dose.

258. I understand that claim 20 depends from claim 17, which depends from claim 16, which depends from claim 15. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan's marketing of YESAFILI in accordance with its proposed labeling will induce infringement of claim 17 of the '572 patent. I incorporate the analysis of claim 17 as though fully set forth herein.

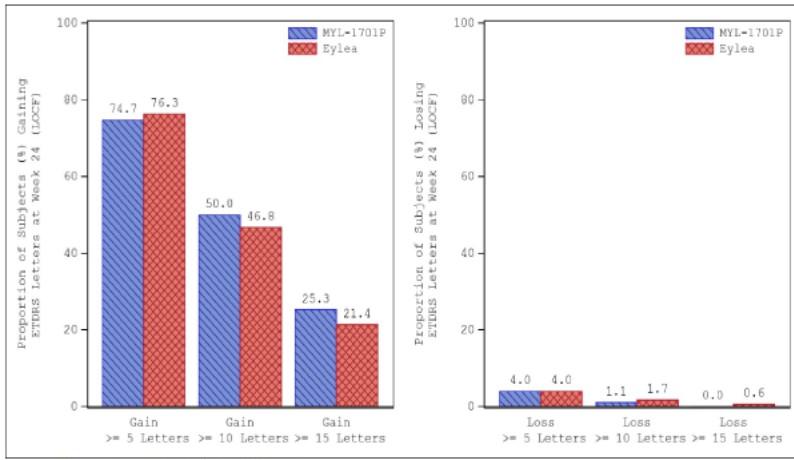
259. In addition, Mylan's marketing of YESAFILI will induce physicians to perform the method of claim 17 *and* the further limitation of claim 20, "wherein the patient achieves a gain in visual acuity within 24 weeks following the initial dose."

260. Mylan reported the week 24 results of its Phase III clinical study in patients with DME using YESAFILI™ to the FDA, as part of its BLA.³⁰¹ That data demonstrates that when YESAFILI™ is administered according to the method of claim 15, patients gained more than 9 letters of BCVA according to ETDRS Letter Score within 24 weeks of the initial dose. In particular, Mylan's clinical study reported that at 24 weeks, doctors measured a gain of more

³⁰¹ MYL-AFL-BLA0552809.

than 10 letters in 50.0% of patients to whom they administered YESAFILI™ according to Mylan's study protocol.³⁰²

Figure 9: Proportion of Subjects Who Gained or Lost ≥5, ≥10 or ≥15 Letters, at Week 24



Source: Figure 14.2.2.4.1a; Listing 16.2.6.5a

261. Furthermore, I have reviewed the individual patient efficacy results, and have identified several patients to whom doctors administered YESAFILI™ in accordance with the method of claim 15 and then measured a gain of more than 9 letters BCVA according to ETDRS within 24 weeks of the initial dose.³⁰³ Examples include patients 110003, 110012, 117013, 202003, and 203007.³⁰⁴

262. This data, which Mylan has presented to the FDA as part of its BLA,³⁰⁵ demonstrates that if Mylan markets YESAFILI™ according to its proposed labeling, doctors will in fact perform the method of claim 15 to treat DME, *and* measure a BCVA gain of at least 9 letters ETDRS within 24 weeks of the initial dose.

³⁰² MYL-AFL-BLA1056844 at -6950; MYL-AFL0089391 at -89399.

³⁰³ *Supra* Section VI.D.e.1.ii.

³⁰⁴ *Supra* Section VI.D.e.1.ii.

³⁰⁵ MYL-AFL-BLA1056844 at -6950; MYL-AFL0089391 at -89399.

263. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 17, “wherein the patient achieves a gain in visual acuity within 24 weeks following the initial dose.” Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 17 and the further limitation of claim 20, “wherein the patient achieves a gain in visual acuity within 24 weeks following the initial dose”, and specifically intends this infringing activity of claim 20.

264. I also incorporate by reference my analysis with respect to Claim 2 above with respect to BCVA, ETDRS, and the fact that such claims are not limited to clinical trials.³⁰⁶ That analysis applies equally to this claim. For the same reasons I explained with respect to claim 2, the POSA would not understand this claim to require measurement of a gain of 9 letters BCVA within 24 weeks of the initial dose using an ETDRS chart; the POSA would instead understand this claim to require measuring a gain in BCVA that is equivalent to 9 letters BCVA according ETDRS letter score, and would understand that such a gain can be measured by performing any appropriate visual acuity testing protocol (e.g., Snellen).³⁰⁷ Regardless, even were this claim interpreted to require measurement using an ETDRS chart, it is still my opinion that Mylan induces infringement of this claim for the same reasons I explained with respect to claim 2 above—namely, because physicians do in fact use ETDRS charts in clinical practice to measure visual acuity gain (I myself have done so), and physicians will use ETDRS charts to measure gains of 9 letters BCVA within 24 weeks of the initial dose according to EDTRS if Mylan markets YESAFILI™ according to its proposed labeling, just as Mylan’s proposed labeling

³⁰⁶ *Supra* Sections VI.D.4.a, VI.D.4 b, and VI.D.4c.

³⁰⁷ *Supra* Section VI.D.4.b.1.

recommends, encourages, and promotes.³⁰⁸ Furthermore, even were this claim interpreted to require use of an ETDRS chart, or an ETDRS protocol, to measure visual acuity, Mylan would induce infringement of this claim under the doctrine of equivalents, for all the reasons I explained above with respect to claim 2.³⁰⁹ Again, for all the reasons I explained with respect to claim 2, this claim is not limited to the performance of its method in clinical trials, and the POSA would not understand the reference to ETDRS and BCVA to mean that the method of this claim can only be performed during clinical trials.³¹⁰ Finally, in the event the Court interprets this claim to not require the physician to perform the step of measuring a gain in visual acuity, I likewise conclude that Mylan would induce infringement of this claim, because if Mylan markets YESAFILI™ in accordance with its approved labeling, at least one physician will perform the steps of claim 15 with respect to a patient who experiences a gain of at least 9 letters BCVA within 24 weeks of the initial dose, and Mylan's proposed labeling recommends, encourages and promotes this conduct.

265. I also incorporate by reference my analysis of claim 20 in the claim charts appended hereto as Appendix C as though set forth fully herein.

23. Claim 21

266. Claim 21 of the '572 patent recites:

21. The method of claim 16 wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

³⁰⁸ *Supra* Section VI.4.b.2.

³⁰⁹ *Supra* Section VI.4.b.3.

³¹⁰ *Supra* Section VI.D.4.d.

267. I understand that claim 21 depends from claim 16, which depends from claim 15.

I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan's marketing of YESAFILI in accordance with its proposed labeling will induce infringement of claim 16 of the '572 patent. I incorporate the analysis of claim 16 as though fully set forth herein.

268. In addition, Mylan's marketing of YESAFILITM will induce physicians to perform the method of claim 16 *and* the further limitation of claim 21, "wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score."

269. As I explained above, Mylan reported the results of its Phase III clinical trial in patients with DME using YESAFILITM to the FDA, as part of its BLA, and to doctors at conferences like AAO. *Supra* Section III.D.3I. I incorporate that analysis as though set forth herein. That data demonstrates that when YESAFILITM is administered according to the method of claim 16, patients gained more than 8 letters of BCVA according to ETDRS Letter Score within 52 weeks of the initial dose. In particular, Mylan's clinical study reported that doctors measured a gain of more than 10 letters in 57.4% of patients to whom they administered YESAFILITM according to Mylan's study protocol.³¹¹ Furthermore, I have reviewed the individual patient efficacy results, and have identified several patients to whom doctors administered YESAFILITM in accordance with the method of claim 1 and then measured a gain

³¹¹ MYL-AFL-BLA1056844 at -6950; MYL-AFL0089391 at -89399.

of more than 8 letters BCVA according to ETDRS within 52 weeks of the initial dose.³¹²

Examples include patients 110003, 110012, 117013, 202003, and 203007.³¹³

270. This data, which Mylan has presented both to the FDA as part of its BLA and to doctors at conferences,³¹⁴ demonstrates that if Mylan markets YESAFILI according to its proposed labeling, doctors will in fact perform the method of claim 16, *and* measure a BCVA gain of at least 8 letters ETDRS within 52 weeks of the initial dose.

271. By marketing YESAFILITM with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 16, “wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.” Indeed, by marketing YESAFILITM with its proposed labeling, Mylan knows that physicians will perform the method of claim 16 and the further limitation of claim 21, “wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score”, and specifically intends this infringing activity of claim 21.

272. I also incorporate by reference my analysis with respect to Claim 2 above with respect to BCVA, ETDRS, and the fact that such claims are not limited to clinical trials.³¹⁵ That analysis applies equally to this claim. For the same reasons I explained with respect to claim 2, the POSA would not understand this claim to require measurement of a gain of 8 letters BCVA

³¹² *Supra* Section VI.D.e.1.ii.

³¹³ *Supra* Section VI.D.e.1.ii.

³¹⁴ MYL-AFL-BLA1056844 at -6950; MYL-AFL0089391 at -89399.

³¹⁵ *Supra* Sections VI.D.4.a, VI.D.4 b, and VI.D.4c.

within 52 weeks of the initial dose using an ETDRS chart; the POSA would instead understand this claim to require measuring a gain in BCVA that is equivalent to 8 letters BCVA according ETDRS letter score, and would understand that such a gain can be measured by performing any appropriate visual acuity testing protocol (e.g., Snellen).³¹⁶ Regardless, even were this claim interpreted to require measurement using an ETDRS chart, it is still my opinion that Mylan induces infringement of this claim for the same reasons I explained with respect to claim 2 above—namely, because physicians do in fact use ETDRS charts in clinical practice to measure visual acuity gain (I myself have done so), and physicians will use ETDRS charts to measure gains of 8 letters BCVA within 52 weeks of the initial dose according to EDTRS if Mylan markets YESAFILI™ according to its proposed labeling, just as Mylan’s proposed labeling recommends, encourages, and promotes.³¹⁷ Furthermore, even were this claim interpreted to require use of an ETDRS chart, or an ETDRS protocol, to measure visual acuity, Mylan would induce infringement of this claim under the doctrine of equivalents, for all the reasons I explained above with respect to claim 2.³¹⁸ Again, for all the reasons I explained with respect to claim 2, this claim is not limited to the performance of its method in clinical trials, and the POSA would not understand the reference to ETDRS and BCVA to mean that the method of this claim can only be performed during clinical trials.³¹⁹ Finally, in the event the Court interprets this claim to not require the physician to perform the step of measuring a gain in visual acuity, I likewise conclude that Mylan would induce infringement of this claim, because if Mylan markets

³¹⁶ *Supra* Section VI.D.4.b.1.

³¹⁷ *Supra* Section VI.4.b.2.

³¹⁸ *Supra* Section VI.4.b.3.

³¹⁹ *Supra* Section VI.D.4.d.

YESAFILI™ in accordance with its approved labeling, at least one physician will perform the steps of claim 15 with respect to a patient who experiences a gain of at least 8 letters BCVA within 52 weeks of the initial dose, and Mylan's proposed labeling recommends, encourages and promotes this conduct.

273. I also incorporate by reference my analysis of claim 21 in the claim charts appended hereto as Appendix C as though set forth fully herein.

24. Claim 22

274. Claim 22 of the '572 patent recites:

22. The method of claim 21 wherein the aflibercept is formulated as an isotonic solution.

275. I understand that claim 22 depends from claim 21, which depends from claim 16, which depends from claim 15. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 21 of the '572 patent. I incorporate that analysis as though fully set forth herein.

276. In addition, Mylan's marketing of YESAFILI will induce physicians to perform the method of claim 21 *and* the further limitation of claim 22, "wherein the aflibercept is formulated as an isotonic solution."

277. I am informed that another of Regeneron's experts, Dr. Bernhardt L. Trout, has offered the opinion that YESAFILI™ is formulated as an isotonic solution." I have been informed that Dr. Trout has analyzed Mylan's formulation of YESAFILI™ (aflibercept-jbv) and concluded that YESAFILI™ (aflibercept-jbv) is formulated as an isotonic solution. I accept and adopt this conclusion and, on that basis, understand the performance of the method of claim 3 using YESAFILI™ to meet every limitation of claim 22.

278. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 21 using aflibercept “wherein the aflibercept is formulated as an isotonic solution,” as claim 22 requires. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 21 using aflibercept “wherein the aflibercept is formulated as an isotonic solution”, and specifically intends this infringing activity of claim 22.

279. I also incorporate by reference my analysis of claim 22 in the claim charts appended hereto as Appendix C as though set forth fully herein.

25. Claim 23

280. Claim 23 of the '572 patent recites:

23. The method of claim 21 wherein the aflibercept is formulated with a nonionic surfactant.

281. I understand that claim 22 depends from claim 21, which depends from claim 16, which depends from claim 15. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 21 of the '572 patent. I incorporate the analysis of claim 21 as though fully set forth herein.

282. In addition, Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 21 *and* the further limitation of claim 23, “wherein the aflibercept is formulated with a nonionic surfactant.”

283. I am informed that another of Regeneron's experts, Dr. Bernhardt L. Trout, has offered the opinion that YESAFILI™ is formulated with a nonionic surfactant. I have been informed that Dr. Trout has analyzed Mylan's formulation of YESAFILI™ (aflibercept-jbvf) and

concluded that YESAFILI™ (aflibercept-jbvf) is formulated with a nonionic surfactant. I accept and adopt this conclusion and, on that basis, understand the performance of the method of claim 21 using YESAFILI™ to meet every limitation of claim 23.

284. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 21 using aflibercept “wherein the aflibercept is formulated with a nonionic surfactant,” as claim 23 requires. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 3 using aflibercept “wherein the aflibercept is formulated as with a nonionic surfactant”, and specifically intends this infringing activity of claim 23.

285. I also incorporate by reference my analysis of claim 23 in the claim charts appended hereto as Appendix C as though set forth fully herein.

26. Claim 25

286. Claim 25 of the '572 patent recites:

25. The method of claim 15 wherein four secondary doses are administered to the patient.

287. I understand that claim 25 depends from claim 15. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 15 of the '572 patent. I incorporate the analysis of claim 15 as though fully set forth herein.

288. In addition, Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 15 *and* the further limitation of claim 25, “wherein four secondary doses are administered to the patient.”

289. It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to treat DME by administering an “initial” dose of 2 mg Eylea® (aflibercept), followed by four

“secondary” doses of 2 mg Eylea® (aflibercept), followed by one or more “tertiary” doses of 2 mg Eylea® (aflibercept).

290. Specifically, the Eylea® label instructs physicians to treat the angiogenic eye disorder of DME by administering 2 mg of Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”³²⁰

291. Accordingly, the Eylea® label instructs physicians to treat DME by administering a single “initial” dose of 2 mg aflibercept, followed by a “secondary” dose of 2 mg Eylea® (aflibercept) four weeks later, followed by another “secondary” dose of 2 mg Eylea® (aflibercept) four weeks after that, followed by a third “secondary” dose of 2 mg Eylea® (aflibercept) four weeks after that, followed by a fourth “secondary” dose of 2 mg Eylea® (aflibercept) four weeks after that, followed by a tertiary dose of 2 mg Eylea® (aflibercept) eight weeks after that, followed by additional “tertiary” doses of 2 mg Eylea® at 8 week intervals thereafter.

292. In other words, when the Eylea® label instructs a physician to administer 2 mg Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections”, before switching to dosing once every 8 weeks, it expressly instructs physicians to administer “a single initial dose of 2 mg of aflibercept”, followed by *four* secondary doses of 2 mg of aflibercept,” before transitioning to tertiary doses.

293. A physician practicing the dosing regimen instructed by Eylea’s® label for the treatment of DME would meet this limitation of claim 26, and a physician administering YESAFILI™ in the same manner would also meet this limitation.

³²⁰ Eylea® Label (2022) at 1-2.

294. Further, the proposed labeling for YESAFILI™ instructs physicians to administer YESAFILI™ in exactly the same way as Eylea®. Specifically, the YESAFILI™ label instructs physicians to treat the angiogenic eye disorder of AMD by administering 2 mg of YESAFILI™ (aflibercept-jbvf) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”³²¹

295. Accordingly, the YESAFILI™ label instructs physicians to treat the angiogenic eye disorder DME by administering a single “initial” dose of 2 mg aflibercept-jbvf, followed by a “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks later, followed by another “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks after that, followed by a third “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks after that, followed by a fourth “secondary” dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks after that, followed by a tertiary dose of 2 mg YESAFILI™ (aflibercept-jbvf) eight weeks after, followed by additional “tertiary” doses of 2 mg Eylea® at 8 week intervals thereafter.

296. In other words, when the YESAFILI™ label instructs a physician to administer 2 mg YESAFILI™ (aflibercept-jbvf) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections”, before switching to dosing once every 8 weeks, it expressly instructs physicians to administer “a single initial dose of 2 mg of aflibercept”, followed by *four* secondary doses of 2 mg of aflibercept,” before transitioning to tertiary doses.³²²

³²¹ MYL-AFL-BLA1079688 at -1079688 to -1079689.

³²² MYL-AFL-BLA1079688 at -1079688 to -1079689.

297. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 15 and the further limitation of claim 25, “wherein four secondary doses are administered to the patient.” Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 15 and the further limitation of claim 25, “wherein four secondary doses are administered to the patient.”, and specifically intends this infringing activity of claim 25.

298. I also incorporate by reference my analysis of claim 25 in the claim charts appended hereto as Appendix C as though set forth fully herein.

27. Claim 26

299. Claim 26 of the '572 patent recites:

26. A method of treating age related macular degeneration in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;

wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and

wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose;

wherein the method is as effective in achieving a gain in visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose.

300. Claim 26 of the '572 patent contains five limitations, each of which I address in turn below:

- (26pre) A method of treating age related macular degeneration in a patient in need thereof comprising

- (26a) sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;
- (26b) wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and
- (26c) wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose
- (26d) wherein the method is as effective in achieving a gain in visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose.

301. Limitations (26pre) to (26c) are substantially identical to limitations (1pre) to (1c), except that (26pre) is limited to treatment of AMD, rather than any the broader category of “treating an angiogenic eye disorder” in claim 1. As I explained above, physicians will perform (1pre) to (1c) *as part of a method to treat AMD in a patient in need thereof*.³²³ I incorporate this analysis by reference as though set forth herein. Accordingly, if Mylan markets YESAFILI™ with its proposed labeling, physicians will perform steps (26pre) through (26c).

302. Step (26d) requires that physicians must perform steps (26pre) through (26d), and measure a gain in visual acuity at least as great as the gain experienced by human subjects receiving monthly administration of 0.5 mg of ranibizumab by intravitreal injection.

³²³ Section VI.D.3.a-VI.D.3.d.

303. Ranibizumab is the active ingredient in Lucentis®. As the specification of the Yancopoulos patent reports, some human subjects in the Phase III studies for Eylea® in DME (*i.e.*, VIEW 1 and VIEW 2) received monthly injections of 0.5 mg Lucentis® for up to 24 months.³²⁴ The highest average gain reported after 52 weeks for such patients in these studies was 9.4 letters BCVA according to ETDRS letter score.³²⁵

304. Mylan's proposed labeling instructs doctors to use YESAFILI™ in the same way they would use Eylea®, and that YESAFILI™ is clinically equivalent to Eylea® when used according to its label.³²⁶ I have treated patients using Eylea® in my own clinical practice, using an initial dose of 2 mg Eylea®, two secondary doses of 2 mg Eylea® two weeks after the immediately preceding dose, and then tertiary doses of 2 mg Eylea® four weeks after the immediately preceding dose. I would measure the BCVA of such patients before every injection, and I have measured BCVA gains of at least 10 letters according to ETDRS Letter Score in such patients within 52 weeks of the initial dose. On this basis, in combination with Mylan's instruction to doctors that YESAFILI is clinically equivalent to Eylea®, I conclude that if Mylan markets YESAFILI™ according to its proposed labeling, doctors will in fact perform steps (26pre) through (26c) *and* measure BCVA gains of at least 10 letters according to ETDRS letter score within 52 weeks of the initial dose, just as claim 26 requires.

305. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 26. Indeed, by marketing YESAFILI™ with its

³²⁴ '572 Patent at Example 4 (9:29-14:31); *see also* '572 Patent at Table 1.

³²⁵ '572 Patent at Table 1 (column 13).

³²⁶ *Supra* section VI.D.2.

proposed labeling, Mylan knows that physicians will perform the method of claim 26, and specifically intends this infringing activity of claim 26.

306. In the event the Court interprets this claim to not require the physician to perform the step of measuring a gain in visual acuity, I likewise conclude that Mylan would induce infringement of this claim, because if Mylan markets YESAFILI™ in accordance with its approved labeling, at least one physician will perform limitations (26pre) through (26d) with respect to a patient who experiences claim 26's required gain in visual acuity, and Mylan's proposed labeling recommends, encourages and promotes this conduct.

307. I also incorporate by reference my analysis of claim 26 in the claim charts appended hereto as Appendix C as though set forth fully herein.

28. Claim 27

308. Claim 27 of the '572 patent recites:

27. The method of claim 26 wherein only two secondary doses are administered to the patient.

309. I understand that claim 27 depends from claim 26. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As I described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 26 of the '572 patent. I incorporate the analysis of claim 26 as though fully set forth herein.

310. In addition, Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 26 *and* the additional limitation of claim 27, "wherein only two secondary doses are administered to the patient." Indeed, my analysis of infringement of claim 26 presumed that the method of claim 26 was being performed using only two secondary doses. I

therefore incorporate by reference my analysis with respect to claim 26 as though set forth herein.

311. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 26 *and* the additional limitation of claim 27 , “wherein only two secondary doses are administered to the patient.” Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 26 *and* the additional limitation of claim 27, “wherein only two secondary doses are administered to the patient”, and specifically intends this infringing activity of claim 27.

312. I also incorporate by reference my analysis of claim 27 in the claim charts appended hereto as Appendix C as though set forth fully herein.

29. Claim 28

313. Claim 28 of the '572 patent recites:

28. The method of claim 26 wherein the gain in visual acuity is measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

314. I understand that claim 28 depends from claim 26. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. As I described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 26 of the '572 patent. I incorporate the analysis of claim 26 as though fully set forth herein.

315. Indeed, my analysis of infringement of claim 26 rested upon an analysis of gains in visual acuity being measured according to the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score. I therefore incorporate by reference my analysis with respect to claim 26 as though set forth herein.

316. By marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 26 *and* the additional limitation of claim 28, “wherein the gain in visual acuity is measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.” By marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 26 *and* the additional limitation of claim 28, “wherein the gain in visual acuity is measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score,” and specifically intends this infringing activity of claim 28.

317. I also incorporate by reference my analysis with respect to Claim 2 above with respect to BCVA, ETDRS, and the fact that such claims are not limited to clinical trials.³²⁷ That analysis applies equally to this claim. Physicians do in fact use ETDRS charts in clinical practice to measure visual acuity gain (I myself have done so), and physicians will use ETDRS charts to measure claim 26’s required gains of in BCVA using EDTRS letter score if Mylan markets YESAFILI™ according to its proposed labeling, just as Mylan’s proposed labeling recommends, encourages, and promotes.³²⁸ Furthermore, in the event Mylan is not found to induce literal infringement of claim 26, Mylan will induce infringement of this claim under the doctrine of equivalents, for all the reasons I explained above with respect to claim 2.³²⁹ In addition, for all the reasons I explained with respect to claim 2, this claim is not limited to the performance of its method in clinical trials, and the POSA would not understand the reference to

³²⁷ *Supra* Sections VI.D.4.a, VI.D.4 b, and VI.D.4c.

³²⁸ *Supra* Section VI.4.b.2.

³²⁹ *Supra* Section VI.4.b.3.

ETDRS and BCVA to mean that the method of this claim can only be performed during clinical trials.³³⁰ Finally, in the event the Court interprets this claim to not require the physician to perform the step of measuring a gain in visual acuity, I likewise conclude that Mylan would induce infringement of this claim, because if Mylan markets YESAFILI™ in accordance with its approved labeling, at least one physician will perform the steps of claim 26 with respect to a patient who experiences claim 26's required gain using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score, and Mylan's proposed labeling recommends, encourages and promotes this conduct.

318. I also incorporate by reference my analysis of claim 28 in the claim charts appended hereto as Appendix C as though set forth fully herein.

E. Mylan Induces Infringement of the '601 Patent

1. The Asserted Claims of the '601 Patent

319. I am informed that Regeneron is asserting claims 5–9, 11, 15–17, 19, 21, 23–25, 27–28 and 31–33 of the '601 Patent. I have reproduced the claims of the '601 patent below, and highlighted the asserted claims.

³³⁰ *Supra* Section VI.D.4.d.

What is claimed is:

1. A method for treating age related macular degeneration in a patient in need thereof, comprising intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 3 months, followed by 2 mg approximately once every 8 weeks or once every 2 months.

2. The method of claim 1, wherein the age-related macular degeneration is neovascular (wet).

3. The method of claim 2 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

4. The method of claim 3 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

5. The method of claim 2 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

6. The method of claim 5 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

7. The method of claim 1, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

8. The method of claim 7, wherein the age-related macular degeneration is neovascular (wet).

9. The method of claim 8 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

40 10. A method for treating diabetic macular edema in a patient in need thereof, comprising intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months.

45 11. The method of claim 10, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

50 12. The method of claim 10, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

55 13. The method of claim 10 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

60 14. The method of claim 13 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

65 15. The method of claim 10 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

16. The method of claim 15 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

17. The method of claim 10 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

18. A method for treating diabetic retinopathy in a patient in need thereof, comprising intravitreally administering, to said patient, an effective amount of afibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or 2 months.

19. The method of claim 18, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

20. The method of claim 19 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score. 10

21. The method of claim 18, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of afibercept once every 4 weeks. 15

22. The method of claim 18 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

23. The method of claim 18 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score. 20

24. The method of claim 23 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

25. The method of claim 18 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection. 25

26. A method for treating diabetic retinopathy in a patient with diabetic macular edema, who is in need of such treatment, comprising intravitreally administering, to said patient, an effective amount of afibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or 2 months.

27. The method of claim 26, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

28. The method of claim 26, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of afibercept once every 4 weeks.

29. The method of claim 26 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

30. The method of claim 29 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

31. The method of claim 26 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

32. The method of claim 31 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

33. The method of claim 26 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

34. A method for treating an angiogenic eye disorder in a patient in need thereof, said method comprising administering to the patient an effective sequential dosing regimen of a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered 8 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor which is VEGFR1 and an Ig domain 3 of a second VEGF receptor which is VEGFR2, and a multimerizing component.

35. The method of claim 34 wherein the VEGF antagonist is afibercept.

36. The method of claim 35 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

37. The method of claim 34, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

38. The method of claim 37, wherein the intraocular administration is intravitreal administration.

39. The method of claim 38, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

40. The method of claim 39, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

41. The method of claim 39, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

42. The method of claim 34, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

43. The method of claim 34 wherein the angiogenic eye disorder is age related macular degeneration.

44. The method of claim 43 wherein all doses of VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

45. The method of claim 43 wherein all doses of VEGF antagonist comprise 2.0 mg of the VEGF antagonist.

46. The method of claim 34 wherein the angiogenic eye disorder is diabetic retinopathy.

47. The method of claim 34, wherein the angiogenic eye disorder is diabetic macular edema.

* * * * *

2. Mylan instructs and encourages physicians to use YESAFILIT™ in the same way they use Eylea®

320. As I explained above in Section III.D.2, Mylan instructs and encourages physicians to use YESAFILIT™ in the same way they use Eylea®. I incorporate that analysis here as though set forth herein.

3. Claim 5

321. Claim 5 of the '601 Patent recites:

5. The method of claim 2 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

322. Claim 5 depends from claim 2, and in turn from claim 1 of the '601 Patent. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. Claims 1 and 2 are recited below.

1. A method for treating age related macular degeneration in a patient in need thereof, comprising intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 3 months, followed by 2 mg approximately once every 8 weeks or once every 2 months.

2. The method of claim 1, wherein the age-related macular degeneration is neovascular (wet).

323. I am informed that Regeneron is not asserting claims 1 and 2 in this litigation, but I nonetheless demonstrate below that if Mylan markets YESAFILI™ in accordance with its proposed labeling, physicians will perform the methods of claims 1 and 2, and Mylan directly recommends, encourages, and promotes this result by virtue of its proposed labeling and other conduct.

a) Unasserted Claim 1

324. Claim 1 of the '601 patent contains 3 limitations, set forth below:

- (1pre) A method for treating age related macular degeneration in a patient in need thereof, comprising
- (1a) intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 3 months,
- (1b) followed by 2 mg approximately once every 8 weeks or once every 2 months.

325. By marketing YESAFILI™ in accordance with its proposed labeling, Mylan knows and specifically intends that physicians will perform every limitation of the method of claim 1. I explain the basis for my opinion in further detail below, and in the claim charts appended to this report at Appendix D. I hereby incorporate by reference my analysis in those claim charts as though set forth fully herein.

1) (1pre) A method for treating age related macular degeneration in a patient in need thereof, comprising

326. With respect to the first limitation (also called the preamble)—“A method of treating age related macular degeneration in a patient in need thereof, comprising”—it is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to administer Eylea® to patients in need of treatment for age related macular degeneration, in order to treat age related macular degeneration.³³¹ Specifically, the Eylea® label instructs physicians to administer aflibercept to treat “Neovascular (Wet) Age-Related Macular Degeneration (AMD).”³³² A physician administering YESAFILI™ in the same manner would meet this limitation.

327. Further, Mylan’s proposed YESAFILI™ labeling instructs physicians to administer YESAFILI™ to treat age related macular degeneration.³³³ Specifically, Mylan’s proposed labeling for YESAFILI™ expressly instructs physicians to administer YESAFILI™ to treat “Neovascular (Wet) Age-Related Macular Degeneration (AMD).”³³⁴

³³¹ Eylea® Label (2022) at 1-2.

³³² Eylea® Label (2022) at 1-2.

³³³ MYL-AFL-BLA1079688 at -1079688 to -1089689.

³³⁴ MYL-AFL-BLA1079688 at -1079688 to -1089689.

328. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform limitation (1pre). In other words, if Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will administer YESAFILI™ to treat age related macular degeneration.

329. Mylan's proposed labeling encourages, recommends, and promotes performance of limitation (1pre) by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will administer YESAFILI™ to treat age related macular degeneration consistent with Claim 1 of the '601 Patent, and specifically intends this infringing activity.

330. I incorporate by reference my analysis of this limitation in the claim charts appended hereto as Appendix D as though set forth fully herein.

2) (1a) intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 3 months,

331. Limitation (1a) requires that the physician administer, to the patient in need of treatment for age related macular degeneration, "an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 3 months." It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to administer an effective amount of Eylea® (aflibercept) which is 2 mg approximately every 4 weeks for the first three months in order to treat patients with age related macular degeneration.

332. Specifically, the Eylea® label instructs physicians to treat age related macular degeneration by administering 2 mg of Eylea® (aflibercept) "by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months, followed by 2 mg (0.05

mL) via intravitreal injection once every 8 weeks (2 months).³³⁵ This instruction directs physicians to treat age related macular degeneration by administering a single “initial” dose of 2 mg Eylea® aflibercept, followed by a second dose of 2 mg Eylea® (aflibercept) four weeks later, followed by another dose of 2 mg Eylea® (aflibercept) four weeks after that, before transitioning to dosing every 8 weeks. Each month of the year is approximately 4 weeks long. Thus, the Eylea® label instructs physicians to administer three doses of 2 mg Eylea® (aflibercept), each approximately 4 weeks after the other, for the first three months of Eylea® treatment—the first dose in the first month, the second dose in the second month, and the third dose in the third month.³³⁶ The Eylea® label therefore instructs physicians to administer an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 3 months to treat age related macular degeneration.

333. A physician practicing the dosing regimen instructed by Eylea’s® label for the treatment of AMD would meet this limitation of claim 1, and a physician administering YESAFILI™ in the same manner would also meet this limitation.

334. Further, Mylan’s proposed labeling for YESAFILI™ instructs physicians to treat age related macular degeneration by administering 2 mg of YESAFILI™ (aflibercept-jbvf) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).³³⁷ This instruction directs physicians to treat age related macular degeneration by administering a single “initial” dose of 2 mg YESAFILI™ (aflibercept-jbvf), followed by a

³³⁵ Eylea® Label (2022) at 1-2.

³³⁶ Eylea® Label (2022) at 1-2.

³³⁷ MYL-AFL-BLA1079688 at -1079688 to -1089689.

second dose of 2 mg YESAFILI™ (aflibercept-jbvf) four weeks later, followed by another dose of YESAFILI™ (aflibercept-jbvf) four weeks after that, before transitioning to dosing every 8 weeks. Each month of the year is approximately 4 weeks long. Thus, the YESAFILI™ (label instructs physicians to administer three doses of 2 mg YESAFILI™ (aflibercept-jbvf), each approximately 4 weeks after the other, for the first three months of YESAFILI™ treatment—the first dose in the first month, the second dose in the second month, and the third dose in the third month.³³⁸ The YESAFILI™ label therefore instructs physicians to administer an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 3 months to treat age related macular degeneration.

335. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform limitation (1a). In other words, if Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will administer YESAFILI™ to treat age related macular degeneration by administering an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 3 months to treat age related macular degeneration, and specifically intends this infringing activity.

336. Mylan's proposed labeling encourages, recommends, and promotes performance of limitation (1a) by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will administer YESAFILI™ to treat age related macular degeneration by administering an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 3 months to treat age related macular degeneration.

337. I incorporate by reference my analysis of this limitation in the claim charts appended hereto as Appendix D as though set forth fully herein.

³³⁸ MYL-AFL-BLA1079688 at -1079688 to -1089689.

3) (1b) followed by 2 mg approximately once every 8 weeks or once every 2 months

338. Limitation (1b) requires that the physician follow step (1a) by administering, to the patient in need of treatment for age related macular degeneration, “2 mg [aflibercept] approximately once every 8 weeks or once every 2 months.” It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to follow three monthly doses of Eylea® with 2 mg Eylea® approximately once every 8 weeks or once every 2 months in order to treat patients with age related macular degeneration.

339. Specifically, the Eylea® label instructs physicians to treat age related macular degeneration by administering 2 mg of Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”³³⁹ This instruction directs physicians to administer 2mg Eylea® (aflibercept) approximately once every 8 weeks or once every 2 months, after delivering three monthly doses of 2 mg Eylea® (aflibercept), in order to treat age related macular degeneration. The Eylea® label therefore instructs physicians to administer “2 mg [aflibercept] approximately once every 8 weeks or once every 2 months” in order to treat age-related macular degeneration.

340. A physician practicing the dosing regimen instructed by Eylea’s® label for the treatment of AMD would meet this limitation of claim 1, and a physician administering YESAFILI™ in the same manner would also meet this limitation.

341. Further, Mylan’s proposed labeling for YESAFILI™ instructs physicians to treat age related macular degeneration by administering 2 mg of YESAFILI™ (aflibercept-jbvf) “by

³³⁹ Eylea® Label (2022) at 1-2.

intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).³⁴⁰ This instruction directs physicians to administer 2mg YESAFILI™ (aflibercept-jbvf) approximately once every 8 weeks or once every 2 months, after delivering three monthly doses of 2 mg YESAFILI™ (aflibercept-jbvf), in order to treat age related macular degeneration. Thus, the YESAFILI™ label instructs physicians to administer YESAFILI™ (aflibercept-jbvf) approximately once every 8 weeks or 2 months, after administering three monthly doses of 2 mg YESAFILI™ (aflibercept-jbvf).³⁴¹

342. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform limitation (1b). In other words, if Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will administer 2 mg YESAFILI™ approximately once every 8 weeks or once every 2 months (after having administered three monthly doses of YESAFILI™), in order to treat age related macular degeneration.

343. Mylan's proposed labeling encourages, recommends, and promotes performance of limitation (1b) by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will administer 2 mg YESAFILI™ approximately once every 8 weeks or once every 2 months (after having administered three monthly doses of YESAFILI™), in order to treat age related macular degeneration, and specifically intends this infringing activity.

³⁴⁰ MYL-AFL-BLA1079688 at -1079688 to -1089689.

³⁴¹ MYL-AFL-BLA1079688 at -1079688 to -1089689.

344. I incorporate by reference my analysis of this limitation in the claim charts appended hereto as Appendix D as though set forth fully herein.

4) Claim 1 Conclusion

345. For the reasons explained above, if Mylan markets YESAFILI™ according to its proposed labeling, physicians will in fact perform the method of Claim 1.

346. By marketing YESAFILI™ according to its approved labeling, which instructs clinicians to use YESAFILI™ in the same manner as Eylea® and in the manner recited in claim 1, Mylan specifically intends such infringement to occur and knows such infringement will occur. Mylan therefore induces infringement of claim 1 of the '601 patent.

b) Unasserted Claim 2

347. Claim 2 of the '601 Patent recites:

2. The method of claim 1, wherein the age-related macular degeneration is neovascular (wet).

348. I understand that claim 2 depends from claim 1. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 1 of the '601 patent. I incorporate that analysis of claim 1 as though fully set forth herein.

349. Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 1 *and* the further limitation of claim 2, "wherein the age-related macular degeneration is neovascular (wet)," as required by claim 2.".

350. As I explained above, the label for Eylea® and the proposed labeling for YESAFILI™ both instruct physicians to administer aflibercept in accordance with claim 1, for the treatment of "Neovascular (Wet) Age-Related Macular Degeneration (AMD)." ³⁴²

³⁴² *Supra* Section VI.E.3.

351. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform the method of claim 2.

352. Mylan's proposed labeling encourages, recommends, and promotes performance of the method of claim 2 by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 2. By marketing YESAFILI™ according to its approved labeling, which instructs clinicians to use YESAFILI™ in the same manner as Eylea® and in the manner recited in claim 2, Mylan specifically intends such infringement to occur and knows such infringement will occur. Mylan therefore induces infringement of claim 2 of the '601 patent.

353. I incorporate by reference my analysis of claim 2 in the claim charts appended hereto as Appendix D as though set forth fully herein

c) Claim 5 Analysis

354. Claim 5 recites:

5. The method of claim 2 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

1) Analysis Under the Correct Construction of Claim 5

355. I understand that claim 5 depends from claim 2 which in turn depends from claim 1. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 2 of the '601 patent. I incorporate the analysis of claim 2 as though fully set forth herein.

356. The POSA would understand Claim 5 to require a physician to perform the method of claim 2, and then measure a gain of at least 15 letters of BCVA score. For the reasons I explained in Section III.D.3.e and incorporate herein by reference, this limitation requires a physician to perform the active step of measuring a gain of at least 15 letters of BCVA score.

357. Furthermore, when physicians measure visual acuity gains in patients with angiogenic disorders like AMD, they measure BCVA, for all the reasons I explained above in Section III.D.4.a. I incorporate that analysis by reference herein.

358. As I described above, *supra* Section VI.D.3, Mylan's proposed labeling instructs doctors to treat patients with neovascular (wet) AMD in a manner that practices the regimen recited in claim 1 of the '601 patent. Mylan's proposed labeling also instructs doctors to use YESAFILI™ in the same way they would use Eylea®, and that YESAFILI™ is clinically equivalent to Eylea® when used according to its label.³⁴³ I have treated patients for neovascular (wet) AMD using Eylea® in my own clinical practice, with an effective amount of Eylea® (afibercept) which is 2 mg approximately every 4 weeks for the first 3 months, followed by 2 mg approximately once every 8 weeks or once every 2 months. I measure the BCVA of such patients before every injection, and I have measured gains of at least 15 letters of Best Corrected Visual Acuity (BCVA) score in such patients. I also frequently speak with other retinal specialists, and these conversations confirm that other physicians have done the same. On this basis, in combination with Mylan's instruction to doctors that YESAFILI™ is clinically equivalent to Eylea®, I conclude that if Mylan markets YESAFILI™ according to its proposed labeling, doctors will in fact perform the method of claim 2, *and* measure gains of least 15 letters of Best Corrected Visual Acuity (BCVA) score, as required by claim 5.

359. In light of all of the above, Mylan recommends, encourages, and promotes infringement of claim 5 of the '601 patent by recommending, encouraging, and promoting a method of treating neovascular (wet) AMD using YESAFILI™ that meets every limitation of claim 5. If Mylan markets YESAFILI™ with its proposed labeling, physicians will perform acts

³⁴³ *Supra* section VI.D.2.

of direct infringement by treating neovascular (wet) AMD using YESAFILI™ in a manner that meets every limitation of claim 5. Accordingly, the marketing of YESAFILI™ pursuant to Mylan's proposed labeling will induce infringement of claim 5 of the '601 patent.

2) Mylan's Incorrect Interpretations of Claim 5

i. Claim 5 is Not Limited to Clinical Trials

360. I am informed that Mylan argues that claim 5 cannot be practiced outside the confines of a clinical trial, because claim 5 refers to BCVA. Simply put, this is not how the POSA would understand claim 5. BCVA is a concept that applies in patient practice as well as in clinical trials. As I explained above, I measure patients' BCVA in my clinical practice.

ii. Mylan Induces Infringement of Claim 5 Even If Claim 5 Does Not Require An Active Measurement Step

361. I am informed by counsel that Mylan may disagree with my understanding of claim 5, based on Mylan's statement at the parties' claim construction hearing on January 24, 2023. In particular, I understand Mylan may argue that Claim 5 does not add a step to the method of claim 2 because it does not require a physician to measure the BCVA score. Rather, according to Mylan, claim 5 is satisfied whenever a patient being treated for wet AMD achieves a visual acuity gain of at least 15 letters YESAFILI™ after a physician has administered the dosing regimen of claim 1, even if no physician ever measures that gain.

362. Even if I were instructed to apply Mylan's interpretation of the claim, my conclusion about whether Mylan induces infringement of claim 5 of the '601 patent would not be altered. Under Mylan's interpretation, a physician need only perform the remaining limitations of claim 5. As I have explained above, if Mylan markets YESAFILI™ in accordance with its proposed labeling, physicians will perform the method of claim 2, and Mylan's label recommends, encourages, and promotes this conduct. On the basis of the data above in Sections

III.D.3.e.1.i and III.D.3.e.1.ii and Mylan's representations that YESAFILI™ is biosimilar to and/or interchangeable with Eylea®, Mylan specifically intends that the performance of the method of claim 2 will cause physicians to additionally measure a gain of at least 15 letters of Best Corrected Visual Acuity (BCVA) score, as required by claim 5, and it is more likely than not that physicians will in fact do so.

3) Claim 5 Conclusion

363. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform the method of claim 5.

364. Mylan's proposed labeling encourages, recommends, and promotes performance of the method of claim 5 by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 5, and specifically intends this infringing activity. Mylan therefore induces infringement of claim 5.

365. I also incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix D as though set forth fully herein.

4. Claim 6

366. Claim 6 of the '601 patent recites:

6. The method of claim 5 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

367. I understand that claim 6 depends from claim 5, which depends from claim 2, which depends from claim 1. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 5 of the '601 patent. I incorporate the analysis of claim 5 as though fully set forth herein.

368. Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 5 *and* the further limitation of claim 6, "wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score."

a) Mylan Induces Literal Infringement of Claim 6 Under the Correct Construction of Claim 6

369. For the reasons I explained above in Section III.D.4.b.1, the reference to BCVA and ETDRS in claim 6 does not require that a physician measure a gain of 15 letters in a patient using an ETDRS chart or ETDRS protocol.³⁴⁴ I incorporate my analysis in Section III.D.4.b.1 by reference as though set forth herein.

370. I described above my clinical experience measuring letter gains of at least 15 letters in patients I have treated for neovascular (wet) AMD using Eylea®. These are 15 letters according to ETDRS letter score, whether I measure the gain using a Snellen chart and convert the measurement to ETDRS letter scores, or whether I measure the gain using an ETDRS chart—regardless, the gain I measure is quantifiable as a gain of 15 letters according to ETDRS letter score.³⁴⁵

b) Mylan Induces Literal Infringement of Claim 6 Even If Claim 6 Requires Measurement Using the ETDRS Chart

371. Even assuming, *arguendo*, that claim 6 requires physicians to measure a 15 letter gain and to *perform that measurement using an ETDRS chart* (and to be clear, I disagree that the POSA would understand claim 6 in that way)—it is still my opinion that Mylan's marketing of YESAFILI™ according to its proposed labeling will induce literal infringement of claim 6. Simply put, some physicians perform BCVA measurements using ETDRS charts to measure

³⁴⁴ *Supra* Section VI.D.4.b.1.

³⁴⁵ *Supra* Section VI.E.3.c.1; Section VI.D.4.b.1.

BCVA in their clinical practice. I have done so myself, and I am aware of colleagues who have done the same. If Mylan markets YESAFILI™ in accordance with its proposed labeling, which recommends, encourages, and promotes use of the method of claim 5, some physicians will in fact measure 15 letter gains in BCVA using an ETDRS chart. Mylan recommends, encourages, and promotes this result by virtue of its proposed labeling for YESAFILI™ and its knowledge of clinical practice.

c) Mylan Induces Infringement Under the Doctrine of Equivalents Even If Claim 6 Requires Measurement Using the ETDRS Chart or Using an ETDRS Protocol

372. Alternatively, Mylan's marketing of YESAFILI™ according to its proposed labeling will induce infringement of claim 6 under the doctrine of equivalents even if claim 6 is interpreted to require physicians measure BCVA gains using an ETDRS chart or a more detailed ETDRS protocol. The physician measures the same visual acuity gain regardless of which chart or protocol the physician uses, and may freely convert between Snellen and ETDRS letter score results. Moreover, measuring BCVA using a Snellen chart performs substantially the same function (*i.e.*, measuring the patient's response to treatment in terms of BCVA), in substantially the same way (*i.e.*, using an eye chart and refractive lenses), to achieve substantially the same result (*i.e.*, a measurement of the patient's BCVA that can be used to make treatment decisions) as measuring BCVA using an ETDRS chart or an ETDRS protocol. This is evidenced by the fact that physicians freely convert between Snellen and ETDRS values, as I have described above.

d) Claim 6 Conclusion

373. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform the method of claim 6.

374. Mylan's proposed labeling encourages, recommends, and promotes performance of the method of claim 6 by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 6, and specifically intends this infringing activity. Mylan therefore induces infringement of claim 6.

375. I also incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix D as though set forth fully herein.

5. Claim 7

376. Claim 7 of the '601 Patent recites:

7. The method of claim 1, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

377. I understand that claim 7 depends from claim 1. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 1 of the '601 patent. I incorporate the analysis of claim 1 as though fully set forth herein.

378. In addition, Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 1 *and* the further limitation of claim 7, "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly." It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to administer an effective amount of Eylea® (afibercept) which is 2 mg approximately every month for the first three months in order to treat patients with neovascular (wet) age related macular degeneration.

379. Specifically, the Eylea® label instructs physicians to treat age related macular degeneration by administering 2 mg of Eylea® (afibercept) "by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months, followed by 2 mg (0.05

mL) via intravitreal injection once every 8 weeks (2 months).³⁴⁶ This instruction directs physicians to treat neovascular (wet) age related macular degeneration by administering three doses of 2 mg Eylea® approximately monthly.³⁴⁷ The Eylea® label therefore instructs physicians to administer an effective amount of aflibercept which is 2 mg approximately monthly for the first 3 months to treat neovascular (wet) age related macular degeneration.

380. Further, Mylan's proposed labeling for YESAFILI™ instructs physicians to treat neovascular (wet) age related macular degeneration by administering 2 mg of YESAFILI™ (aflibercept-jbvf) "by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first three months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)."³⁴⁸ This instruction directs physicians to treat neovascular (wet) age related macular degeneration by administering three doses of 2 mg YESAFILI™ (aflibercept-jbvf) approximately monthly.³⁴⁹ The YESAFILI™ label therefore instructs physicians to administer an effective amount of aflibercept which is 2 mg approximately monthly (approximately every 28 days) for the first 3 months to treat neovascular (wet) age related macular degeneration.

381. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform the method of claim 7.

382. Mylan's proposed labeling encourages, recommends, and promotes performance of the method of claim 7 by physicians. Indeed, by marketing YESAFILI™ with its proposed

³⁴⁶ Eylea® Label (2022) at 1-2.

³⁴⁷ Eylea® Label (2022) at 1-2.

³⁴⁸ Eylea® Label (2022) at 1-2.

³⁴⁹ Eylea® Label (2022) at 1-2.

labeling, Mylan knows that physicians will perform the method of claim 7 to treat age related macular degeneration, and specifically intends this infringing activity.

383. I incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix D as though set forth fully herein.

6. Claim 8

384. Claim 8 of the '601 Patent recites:

2. The method of claim 7, wherein the age-related macular degeneration is neovascular (wet).

385. I understand that claim 8 depends from claim 7 which in turn depends from claim 1. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 7 of the '601 patent. I incorporate the analysis of claim 7 as though fully set forth herein.

386. In addition, Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 7 *and* the further limitation of claim 8, "wherein the age-related macular degeneration is neovascular (wet)," as required by claim 8.

387. As I explained above, the label for Eylea® and the proposed labeling for YESAFILI™ both instruct physicians to administer afibercept in accordance with claim 7, for the treatment of "Neovascular (Wet) Age-Related Macular Degeneration (AMD)." ³⁵⁰

388. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform the method of claim 8.

389. Mylan's proposed labeling encourages, recommends, and promotes performance of the method of claim 8 by physicians. Indeed, by marketing YESAFILI™ with its proposed

³⁵⁰ *Supra* Section VI.E.5.

labeling, Mylan knows that physicians will perform the method of claim 8. By marketing YESAFILI™ according to its approved labeling, which instructs clinicians to use YESAFILI™ in the same manner as Eylea® and in the manner recited in claim 8, Mylan specifically intends such infringement to occur and knows such infringement will occur. Mylan therefore induces infringement of claim 2 of the '601 patent.

390. I incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix D as though set forth fully herein

7. Claim 9

391. Claim 9 of the '601 Patent recites:

9. The method of claim 8 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

392. I understand that claim 9 depends from claim 8 which depends from claim 7 which in turn depends from claim 1. The POSA would understand the method of claim 9 to require that a doctor perform a method of treating neovascular (wet) AMD in a patient in need thereof comprising:

- (9a) Assessing the patient for active intraocular inflammation or active ocular or periocular infection
- (9b) If the assessment determines the patient does not have the assessed-for condition, performing the method of claim 8.

393. As I described above in Section III.E.6, if Mylan markets YESAFILI™ in accordance with its proposed label, physicians will perform the method of claim 8. I incorporate the analysis of claim 8 as though set forth herein.

394. In addition, if Mylan markets YESAFILI™ in accordance with its proposed label, physicians will perform the method of *first* assessing the patient for active intraocular

inflammation or active ocular or periocular infection, and *then, if the assessment determines that the patient does not have active intraocular inflammation or active ocular or periocular infection,* performing the method of claim 8.

395. It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to assess patients for active intraocular inflammation or active ocular or periocular infection, and then, on the basis of that assessment, administer Eylea® in accordance with claim 8.³⁵¹

396. Specifically, the Eylea® label lists both “ocular or periocular infection” and “active intraocular inflammation” as contraindications for administration of Eylea®. As the POSA would understand, when a drug label lists conditions under the heading “Contraindications,” that label instructs physicians to assess patients for the presence of the contraindicated condition and to decline to treat patients with the drug that is the subject of the label if that assessment reveals the presence of the contraindicated condition. Accordingly, the Eylea® label instructs physicians to assess patients for active intraocular inflammation and active ocular or periocular infection before administering Eylea®. A physician administering YESAFILI™ in the same manner would meet this limitation.³⁵²

397. Further, Mylan’s proposed YESAFILI™ labeling instructs physicians to assess and adhere to the same contraindications as Eylea’s® label.³⁵³ Specifically, the YESAFILI™

³⁵¹ Eylea® Label (2022) at 4.

³⁵² Eylea® Label (2022) at 4.

³⁵³ MYL-AFL-BLA1079688 at Highlights of Prescribing Information (listing as contraindications “Ocular or periocular infection” and “Active intraocular inflammation”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.1 (“YESAFILI is contraindicated in patients with ocular or periocular infections.”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.2 (“YESAFILI is contraindicated in patients with active intraocular inflammation.”).

label lists both “ocular or periocular infection” and “active intraocular inflammation” as contraindications for administration of YESAFILI™.

398. For the reasons I explained in Section VI.6.D.16.b, the POSA would not understand the method of claim 9 to be limited to performance of a method of treatment in a clinical trial.³⁵⁴ I incorporate that analysis by reference herein.

399. Accordingly, the YESAFILI™ label instructs physicians to assess patients for active intraocular inflammation and active ocular or periocular infection before administering YESAFILI™. In this manner, the YESAFILI™ labeling expressly directs physicians to perform the method of claim 9.

400. Thus, by marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 8 and the additional step of claim 9, “wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection,” as required by claim 9. Indeed, by marketing YESAFILI with its proposed labeling, Mylan knows that physicians will perform the method of claim 8 and the additional step of claim 9, “wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection”, and thus specifically intends this infringing activity of claim 9. Mylan therefore induces infringement of claim 9.

401. I also incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix D as though set forth fully herein.

8. Claim 11

402. Claim 11 recites:

11. The method of claim 10, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

³⁵⁴ *Supra* Section VI.6.D.16.b.

403. Claim 11 depends from claim 10. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend. Claim 10 recites:

10. A method for treating diabetic macular edema in a patient in need thereof, comprising intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months.

404. I am informed that Regeneron is not asserting claim 10 in this litigation, but I nonetheless demonstrate below that if Mylan markets YESAFILI™ in accordance with its proposed labeling, physicians will perform the method of claim 10, and Mylan directly recommends, encourages, and promotes this result by virtue of its proposed labeling and other conduct.

a) Unasserted Claim 10

405. Claim 10 of the '601 patent contains 3 limitations, set forth below:

- (10pre) A method for treating diabetic macular edema in a patient in need thereof
- (10a) intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections,
- (10b) followed by 2 mg approximately once every 8 weeks or once every 2 months.

406. By marketing YESAFILI™ in accordance with its proposed labeling, Mylan knows and specifically intends that physicians will perform every limitation of the method of claim 10. I explain the basis for my opinion in further detail below, and in the claim charts appended to this report at Appendix D. I hereby incorporate by reference my analysis in those claim charts as though set forth fully herein.

1) (10pre) A method for treating diabetic macular edema in a patient in need thereof

407. With respect to the first limitation (also called the preamble)—“A method for treating diabetic macular edema in a patient in need thereof”—it is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to administer Eylea® to patients in need of treatment for diabetic macular edema, in order to treat diabetic macular edema.³⁵⁵ Specifically, the Eylea® label instructs physicians to administer aflibercept to treat “Diabetic Macular Edema (DME).”³⁵⁶ A physician administering YESAFILI™ in the same manner would meet this limitation.

408. Further, Mylan’s proposed YESAFILI™ labeling instructs physicians to administer YESAFILI™ to treat diabetic macular edema.³⁵⁷ Specifically, Mylan’s proposed labeling for YESAFILI™ expressly instructs physicians to administer YESAFILI™ to treat “Diabetic Macular Edema (DME).”³⁵⁸

409. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform limitation (10pre). In other words, if Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will administer YESAFILI™ to treat diabetic macular edema.

410. Mylan’s proposed labeling encourages, recommends, and promotes performance of limitation (10pre) by physicians. Indeed, by marketing YESAFILI™ with its proposed

³⁵⁵ Eylea® Label (2022) at 1-2.

³⁵⁶ Eylea® Label (2022) at 1-2.

³⁵⁷ MYL-AFL-BLA1079688 at -1079688 to -1089689.

³⁵⁸ MYL-AFL-BLA1079688 at -1079688 to -1089689.

labeling, Mylan knows that physicians will administer YESAFILI™ to treat diabetic macular edema consistent with Claim 10 of the '601 Patent, and specifically intends this infringing activity.

411. I incorporate by reference my analysis of this limitation in the claim charts appended hereto as Appendix D as though set forth fully herein.

- 2) **(10a) intravitreally administering, to said patient, an effective amount of afibercept which is 2 mg approximately every 4 weeks for the first 5 injections,**

412. Limitation (10a) requires that the physician “intravitreally administer[], to said patient, an effective amount of afibercept which is 2 mg approximately every 4 weeks for the first 5 injections.” It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to intravitreally administer an effective amount of Eylea® (afibercept) which is 2 mg approximately every 4 weeks for the first five injections in order to treat patients with diabetic macular edema.

413. Specifically, the Eylea® label instructs physicians to treat diabetic macular edema by administering 2 mg of Eylea® (afibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”³⁵⁹ This instruction directs physicians to treat diabetic macular edema by administering five doses of Eylea® each approximately four weeks after the preceding dose, before transitioning to dosing every 8 weeks. Thus, the Eylea®

³⁵⁹ Eylea® Label (2022) at 1-2.

label instructs physicians to “intravitreally administer[] an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections.”³⁶⁰

414. A physician practicing the dosing regimen instructed by Eylea’s® label for the treatment of DME would meet this limitation of claim 10, and a physician administering YESAFILI™ in the same manner would also meet this limitation.

415. Further, Mylan’s proposed labeling for YESAFILI™ instructs physicians to treat diabetic macular edema by administering 2 mg of YESAFILI™ (aflibercept-jbvf) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”³⁶¹ This instruction directs physicians to treat diabetic macular edema by administering five doses of YESAFILI™ (aflibercept-jbvf) each approximately four weeks after the preceding dose, before transitioning to dosing every 8 weeks. Thus, the YESAFILI™ label instructs physicians to “intravitreally administer[] an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections.”³⁶²

416. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform limitation (10a). In other words, if Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will administer YESAFILI™ to treat diabetic macular edema by administering an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections.

³⁶⁰ Eylea® Label (2022) at 1-2.

³⁶¹ MYL-AFL-BLA1079688 at -1079688 to -1089689.

³⁶² MYL-AFL-BLA1079688 at -1079688 to -1089689.

417. Mylan's proposed labeling encourages, recommends, and promotes performance of limitation (10a) by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will administer YESAFILI™ to treat diabetic macular edema by administering an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections.

418. I incorporate by reference my analysis of this limitation in the claim charts appended hereto as Appendix D as though set forth fully herein.

3) (10b) followed by 2 mg approximately once every 8 weeks or once every 2 months.

419. Limitation (10b) requires that the physician follow step (10a) by administering, to the patient in need of treatment for diabetic macular edema, "2 mg [aflibercept] approximately once every 8 weeks or once every 2 months." It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to follow the first five injections of Eylea® with 2 mg Eylea® approximately once every 8 weeks or once every 2 months in order to treat patients with diabetic macular edema.

420. Specifically, the Eylea® label instructs physicians to treat diabetic macular edema by administering 2 mg of Eylea® (aflibercept) "by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)."³⁶³ This instruction directs physicians to administer 2mg Eylea® (aflibercept) approximately once every 8 weeks or once every 2 months, after delivering five monthly of 2 mg Eylea® (aflibercept), in order to treat diabetic macular edema. The Eylea® label therefore instructs physicians to administer "2 mg [aflibercept]

³⁶³ Eylea® Label (2022) at 1-2.

approximately once every 8 weeks or once every 2 months” in order to treat diabetic macular edema.

421. A physician practicing the dosing regimen instructed by Eylea’s® label for the treatment of diabetic macular edema would meet this limitation of claim 10, and physician administering YESAFILI™ in the same manner would also meet this limitation.

422. Further, Mylan’s proposed labeling for YESAFILI™ instructs physicians to treat diabetic macular edema by administering 2 mg of YESAFILI™ (aflibercept-jbvf) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”³⁶⁴ This instruction directs physicians to administer 2mg YESAFILI™ (aflibercept-jbvf) approximately once every 8 weeks or once every 2 months, after delivering five monthly doses of 2 mg YESAFILI™ (aflibercept-jbvf), in order to treat diabetic macular edema. Thus, the YESAFILI™ label instructs physicians to administer (aflibercept-jbvf) approximately once every 8 weeks or 2 months, after administering five injections of 2 mg YESAFILI™ (aflibercept-jbvf). The YESAFILI™ label therefore instructs physicians to administer “2 mg [aflibercept] approximately once every 8 weeks or once every 2 months” in order to treat diabetic macular edema.³⁶⁵

423. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform limitation (10b). In other words, if Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will administer 2 mg YESAFILI™ approximately once every 8 weeks or once every 2 months (after having

³⁶⁴ MYL-AFL-BLA1079688 at -1079688 to -1089689.

³⁶⁵ MYL-AFL-BLA1079688 at -1079688 to -1089689.

administered five injections of 2 mg YESAFILI™ approximately once every four weeks), in order to treat diabetic macular edema.

424. Mylan's proposed labeling encourages, recommends, and promotes performance of limitation (10b) by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will administer 2 mg YESAFILI™ approximately once every 8 weeks or once every 2 months (after having administered five injections of 2mg YESAFILI™ approximately once every four weeks), in order to treat diabetic macular edema.

425. I incorporate by reference my analysis of this limitation in the claim charts appended hereto as Appendix D as though set forth fully herein

4) Claim 10 Conclusion

426. For the reasons explained above, if Mylan markets YESAFILI™ according to its proposed labeling, physicians will in fact perform the method of Claim 10.

427. By marketing YESAFILI™ according to its approved labeling, which instructs clinicians to use YESAFILI™ in the same manner as Eylea® and in the manner recited in claim 10, Mylan specifically intends such infringement to occur and knows such infringement will occur. Mylan therefore induces infringement of claim 10 of the '601 patent.

b) Claim 11 Analysis

11. The method of claim 10, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

428. I understand that claim 11 depends from claim 10. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 10 of the '601 patent. I incorporate the analysis of claim 10 as though fully set forth herein.

429. Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 10 *and* the further limitation of claim 11, "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly." It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to administer an effective amount of Eylea® (aflibercept) which is 2 mg approximately every month for the first five injections in order to treat patients with diabetic macular edema.

430. Specifically, the Eylea® label instructs physicians to treat diabetic macular edema by administering 2 mg of Eylea® (aflibercept) "by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)."³⁶⁶ This instruction directs physicians to treat diabetic macular edema by administering five injections of 2 mg Eylea® approximately monthly.³⁶⁷ The Eylea® label therefore instructs physicians to administer an effective amount of aflibercept which is 2 mg approximately monthly for the first 5 injections to treat diabetic macular edema.

431. A physician practicing the dosing regimen instructed by Eylea's® label for the treatment of diabetic macular edema would meet this limitation of claim 10, and physician administering YESAFILI™ in the same manner would also meet this limitation.

432. Further, Mylan's proposed labeling for YESAFILI™ instructs physicians to treat diabetic macular edema by administering 2 mg of YESAFILI™ (aflibercept-jbvf) "by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5

³⁶⁶ Eylea® Label (2022) at 1-2.

³⁶⁷ Eylea® Label (2022) at 1-2.

injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).³⁶⁸ This instruction directs physicians to treat diabetic macular edema by administering five doses of 2 mg YESAFILI™ (aflibercept-jbv) approximately monthly.³⁶⁹ The YESAFILI™ label therefore instructs physicians to administer an effective amount of aflibercept which is 2 mg approximately monthly for the first five injections to treat diabetic macular edema.

433. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform the method of claim 11.

434. Mylan's proposed labeling encourages, recommends, and promotes performance of the method of claim 11 by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 11 to treat diabetic macular edema, and specifically intends this infringing activity.

435. I incorporate by reference my analysis of claim 11 in the claim charts appended hereto as Appendix D as though set forth fully herein.

9. Claim 12

436. Claim 12 recites:

12. The method of claim 10, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

437. I understand that claim 12 depends from claim 10. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 10 of the '601 patent. I incorporate the analysis of claim 10 as though fully set forth herein.

³⁶⁸ Eylea® Label (2022) at 1-2.

³⁶⁹ Eylea® Label (2022) at 1-2.

438. Furthermore, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce physicians to perform the method of claim 10 *and* the further limitation of claim 12, "further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks."

439. By administering YESAFILI™ according to the method of claim 10, a physician administers 2 mg aflibercept for the first 5 injections—*i.e.*, injections at baseline (week 0), and weeks 4, 8, 12, and 16; the physician then follows with a 2 mg dose at approximately 8 weeks thereafter (*i.e.*, after week 24). Claim 12 requires that the physician then revert to monthly dosing, and administer doses of aflibercept at approximately week 28 and week 32.

440. YESAFILI™'s proposed labeling recommends, encourages, and promotes such conduct in certain patients under certain circumstances—specifically, the label states that for the treatment of DME, "[s]ome patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months)." As a result of this statement, some doctors will observe the need for every 4 week (monthly) dosing after week 20, and will actually perform such dosing, in accordance with claim 12. Accordingly, Mylan induces infringement of claim 12 of the '601 patent.

441. I incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix D as though set forth fully herein.

10. Claim 15

442. Claim 15 recites:

15. The method of claim 10 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

443. I understand that claim 15 depends from claim 10. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 10 of the '601 patent. I incorporate that analysis as though fully set forth herein.

444. Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 10 *and* the further limitation of claim 15, "wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score."

445. The POSA would understand Claim 15 to require a physician perform the method of claim 10, and then measure a gain of at least 15 letters of BCVA score. For the reasons I explained in Section III.D.3.e and incorporate herein by reference, this limitation requires a physician to perform the active step of measuring measure a gain of at least 15 letters of BCVA score.

446. Furthermore, when physicians measure visual acuity gains in patients with angiogenic disorders like DME, they measure BCVA, for all the reasons I explained above in Section III.D.4.a. I incorporate that analysis by reference herein.

447. Mylan's proposed labeling instructs doctors to use YESAFILI™ in the same way they would use Eylea®, and that YESAFILI™ is clinically equivalent to Eylea® when used according to its label.³⁷⁰ I have treated patients with DME using Eylea® in my own clinical practice, by intravitreally administering, to said patient, an effective amount of afibercept which is 2 mg approximately every 4 weeks for the first 5 injections, followed by 2 mg approximately once every 8 weeks or once every 2 months. I measure the BCVA of such patients before every injection, and I have measured gains of at least 15 letters of Best Corrected Visual Acuity (BCVA) score. I also frequently speak with other retinal specialists, and these conversations confirm that other physicians have done the same. On this basis, in combination with Mylan's instruction to doctors that YESAFILI™ is clinically equivalent to Eylea®, I conclude that if Mylan markets YESAFILI™ according to its proposed labeling, doctors will in fact perform the

³⁷⁰ *Supra* section VI.D.2.

method of claim 10 in order to treat DME, *and* measure BCVA gains according to ETDRS letter score, as required by claim 15.

448. In addition, Mylan presented the results of its phase III study in patients with DME, where 33% of patients treated with YESAFILI™ achieved a gain of at least 15 letters 52 weeks after their initial dose.³⁷¹ including the gains in BCVA that physicians measured in individual patients. Above, I provided examples of several patients to whom physicians administered the regimen of claim 10 and in whom physicians measured a gain of at least 15 letters of Best Corrected Visual Acuity (BCVA) during Mylan's DME trial—*i.e.*, patients 110003, 110012, and 203007.³⁷²

449. Mylan's data—submitted as part of its BLA—demonstrates that by marketing YESAFILI™ with its proposed labeling, direct infringement will occur. That is, Mylan's data demonstrate that it is more likely than not that one or more clinicians will, in fact, measure a gain in their patients' visual acuity of at least 15 letters of Best Corrected Visual Acuity (BCVA) score, as Claim 15 of the '601 Patent requires. Mylan's submission of this data to FDA (data that it touts to FDA and physicians alike as demonstrating the biosimilarity and clinical equivalence of Eylea® and YESAFILI™), in combination with the fact that its proposed labeling directs physicians to perform the other steps of the method of claim 10 (from which claim 15 depends), shows that Mylan knows such results will occur and specifically intends to induce this infringing activity.

³⁷¹Supra Section VI.D.e.1.ii. Of the patients who received YESAFILI™, 55.9% received a regimen that meets every limitation of claim 1. MYL-AFL-BLA1056844 at -1056950; MYL-AFL-BLA1055435 at -1055473, -1055481 to -1055486 (protocol defining dosing of YESAFILI, and actions taken at each visit).

³⁷² Supra Section VI.D.e.1.ii.

450. In light of all of the above, Mylan recommends, encourages, and promotes infringement of claim 15 of the '601 patent by recommending, encouraging, and promoting a method of treating DME using YESAFILI™ that meets every limitation of claim 15. If Mylan markets YESAFILI™ with its proposed labeling, physicians will perform acts of direct infringement by treating DME using YESAFILI™ in a manner that meets every limitation of claim 15. Accordingly, the marketing of YESAFILI™ pursuant to Mylan's proposed labeling will induce infringement of claim 15 of the '601 patent.

451. In the event the Court interprets this claim to not require the physician to perform the step of measuring a gain in visual acuity, I likewise conclude that Mylan would induce infringement of this claim, because if Mylan markets YESAFILI™ in accordance with its approved labeling, at least one physician will perform the steps of claim 10 with respect to a patient who experiences a gain of at least 15 letters of BCVA score, and Mylan's proposed labeling recommends, encourages and promotes this conduct.

452. I incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix D as though set forth fully herein.

11. Claim 16

453. Claim 16 recites:

16. The method of claim 15 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

454. I understand that claim 16 depends from claim 15 which in turn depends from claim 10. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 15 of the '601 patent. I incorporate the analysis of claim 15 as though fully set forth herein.

455. In addition, Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 15 and the further limitation of claim 16, "wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score".

c) Mylan Induces Literal Infringement of Claim 16 Under the Correct Construction of Claim 16

456. For the reasons I explained above in connection with Claim 2 of the '572 Patent, claim 16 does not require that a physician measure a gain of 15 letters in a patient using an ETDRS chart or ETDRS protocol.³⁷³ I incorporate that analysis by reference as though set forth herein.

457. I described above my clinical experience measuring letter gains of at least 15 letters in patients I treat for DME using Eylea®.³⁷⁴ These are 15 letters according to ETDRS letter score, whether I measure the gain using a Snellen chart and convert the measurement to ETDRS letter scores, or whether I measure the gain using an ETDRS chart—regardless, the gain I measure is quantifiable as a gain of 15 letters according to ETDRS letter score.³⁷⁵

d) Mylan Induces Literal Infringement of Claim 16 Even If Claim 16 Requires Measurement Using the ETDRS Chart

458. Even assuming, *arguendo*, that claim 16 requires physicians to measure a 15 letter gain and to *perform that measurement using an ETDRS chart* (and to be clear, I disagree that the POSA would understand claim 16 in that way)—it is still my opinion that Mylan's marketing of YESAFILI™ according to its proposed labeling will induce literal infringement of claim 16.

³⁷³ *Supra* Section VI.D.4.b.1.

³⁷⁴ *Supra* Section VI.E.9.

³⁷⁵ *Supra* Section VI.E.9; Section VI.D.4.b.1.

Simply put, some physicians perform BCVA measurements using ETDRS *charts* to measure BCVA in their clinical practice. I have done so myself, and I am aware of colleagues who have done the same. If Mylan markets YESAFILI™ in accordance with its proposed labeling, which recommends, encourages, and promotes use of the method of claim 16, some physicians will in fact measure 15 letter gains in BCVA using an ETDRS chart. Mylan recommends, encourages, and promotes this result by virtue of its proposed labeling for YESAFILI™ and its knowledge of clinical practice.

e) Mylan Induces Infringement Under the Doctrine of Equivalents Even If Claim 16 Requires Measurement Using the ETDRS Chart or Using an ETDRS Protocol

459. Alternatively, Mylan's marketing of YESAFILI™ according to its proposed labeling will induce infringement of claim 16 under the doctrine of equivalents even if claim 16 is interpreted to require physicians measure BCVA gains using an ETDRS chart or a more detailed ETDRS protocol. The physician measures the same visual acuity gain regardless of which chart or protocol the physician uses, and may freely convert between Snellen and ETDRS letter score results. Moreover, measuring BCVA using a Snellen chart performs substantially the same function (*i.e.*, measuring the patient's response to treatment in terms of BCVA), in substantially the same way (*i.e.*, using an eye chart and refractive lenses), to achieve substantially the same result (*i.e.*, a measurement of the patient's BCVA that can be used to make treatment decisions) as measuring BCVA using an ETDRS chart or an ETDRS protocol. This is evidenced by the fact that physicians freely convert between Snellen and ETDRS values, as I have described above.

f) Claim 16 Conclusion

460. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform the method of claim 16.

461. Mylan's proposed labeling encourages, recommends, and promotes performance of the method of claim 16 by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 16, and specifically intends this infringing activity. Mylan therefore induces infringement of claim 16.

462. I also incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix D as though set forth fully herein

12. Claim 17

463. Claim 17 recites:

17. The method of claim 10 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

464. I understand that claim 17 depends from claim 10. The POSA would understand the method of claim 17 to require that a doctor perform a method of treating DME in a patient in need thereof comprising:

- (17a) Assessing the patient for active intraocular inflammation or active ocular or periocular infection
- (17b) If the patient does not have the assessed-for condition, performing the method of claim 10.

465. As I described above in Section III.E.8.a, if Mylan markets YESAFILI™ in accordance with its proposed label, physicians will perform the method of claim 10. I incorporate the analysis of claim 10 as though set forth herein.

466. In addition, if Mylan markets YESAFILI™ in accordance with its proposed label, physicians will perform the method of *first* assessing the patient for active intraocular inflammation or active ocular or periocular infection, and *then, if the assessment determines that*

the patient does not have active intraocular inflammation or active ocular or periocular infection, performing the method of claim 10.

467. It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to assess patients for active intraocular inflammation or active ocular or periocular infection, and then, on the basis of that assessment, administer Eylea® in accordance with claim 10.³⁷⁶

468. Specifically, the Eylea® label lists both “ocular or periocular infection” and “active intraocular inflammation” as contraindications for administration of Eylea®. As the POSA would understand, when a drug label lists conditions under the heading “Contraindications,” that label instructs physicians to assess patients for the presence of the contraindicated condition and to decline to treat patients with the drug that is the subject of the label if that assessment reveals the presence of the contraindicated condition. Accordingly, the Eylea® label instructs physicians to assess patients for active intraocular inflammation and active ocular or periocular infection before administering Eylea®. A physician administering YESAFILI™ in the same manner would meet this limitation.³⁷⁷

469. Further, Mylan’s proposed YESAFILI™ labeling instructs physicians to assess and adhere to the same contraindications as Eylea’s® label.³⁷⁸ Specifically, the YESAFILI™

³⁷⁶ Eylea® Label (2022) at 4.

³⁷⁷ Eylea® Label (2022) at 4.

³⁷⁸ MYL-AFL-BLA1079688 at Highlights of Prescribing Information (listing as contraindications “Ocular or periocular infection” and “Active intraocular inflammation”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.1 (“YESAFILI is contraindicated in patients with ocular or periocular infections.”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.2 (“YESAFILI is contraindicated in patients with active intraocular inflammation.”).

label lists both “ocular or periocular infection” and “active intraocular inflammation” as contraindications for administration of YESAFILI™.

470. For the reasons I explained in Section VI.6.D.16.b, the POSA would not understand the method of claim 17 to be limited to performance of a method of treatment in a clinical trial.³⁷⁹ I incorporate that analysis by reference herein.

471. Accordingly, the YESAFILI™ label instructs physicians to assess patients for active intraocular inflammation and active ocular or periocular infection before administering YESAFILI™. In this manner, the YESAFILI™ labeling expressly directs physicians to perform the method of claim 17.

472. Thus, by marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 10 and the additional step of claim 1717, “wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.” Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 10 and the additional step of claim 17, “wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection”, as required by claim 17, and specifically intends this infringing activity. Mylan therefore induces infringement of claim 17.

473. I also incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix D as though set forth fully herein.

13. Claim 19

474. Claim 19 recites:

19. The method of claim 18, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

³⁷⁹ *Supra* Section VI.6.D.16.b.

475. I understand that claim 19 depends from claim 18. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend.

Claim 18 recites:

18. A method for treating diabetic retinopathy in a patient in need thereof, comprising intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or 2 months.

476. I am informed that Regeneron is not asserting claim 18 in this litigation, but I nonetheless demonstrate below that if Mylan markets YESAFILI™ in accordance with its proposed labeling, physicians will perform the method of claim 18, and Mylan directly recommends, encourages, and promotes this result by virtue of its proposed labeling and other conduct.

a) Unasserted Claim 18

477. Claim 18 contains three limitations, as follows:

- (18pre) A method for treating diabetic retinopathy in a patient in need thereof
- (18a) intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections,
- (18b) followed by 2 mg approximately once every 8 weeks or 2 months.

478. By marketing YESAFILI™ in accordance with its proposed labeling, Mylan knows and specifically intends that physicians will perform every limitation of the method of claim 18. I explain the basis for my opinion in further detail below, and in the claim charts appended to this report at Appendix D. I hereby incorporate by reference my analysis in those claim charts as though set forth fully herein.

1) (18pre) A method for treating diabetic retinopathy in a patient in need thereof

479. With respect to the first limitation (also called the preamble)—“A method for treating diabetic retinopathy in a patient in need thereof”—it is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to administer Eylea® to patients in need of treatment for diabetic retinopathy, in order to treat diabetic retinopathy.³⁸⁰ Specifically, the Eylea® label instructs physicians to administer aflibercept to treat “Diabetic Retinopathy (DR).”³⁸¹ A physician administering YESAFILI™ in the same manner would meet this limitation.

480. Further, Mylan’s proposed YESAFILI™ labeling instructs physicians to administer YESAFILI™ to treat diabetic retinopathy.³⁸² Specifically, Mylan’s proposed labeling for YESAFILI™ expressly instructs physicians to administer YESAFILI™ to treat “Diabetic Retinopathy (DR).”³⁸³

481. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform limitation (18pre). In other words, if Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will administer YESAFILI™ to treat diabetic retinopathy.

482. Mylan’s proposed labeling encourages, recommends, and promotes performance of limitation (18pre) by physicians. Indeed, by marketing YESAFILI™ with its proposed

³⁸⁰ Eylea® Label (2022) at 1-2.

³⁸¹ Eylea® Label (2022) at 1-2.

³⁸² MYL-AFL-BLA1079688 at -1079688 to -1089689.

³⁸³ MYL-AFL-BLA1079688 at -1079688 to -1089689.

labeling, Mylan knows that physicians will administer YESAFILI™ to treat diabetic retinopathy consistent with Claim 18 of the '601 Patent, and specifically intends this infringing activity.

483. I incorporate by reference my analysis of this limitation in the claim charts appended hereto as Appendix D as though set forth fully herein.

- 2) **(18a) intravitreally administering, to said patient, an effective amount of afibercept which is 2 mg approximately every 4 weeks for the first 5 injections,**

484. Limitation (18a) requires that the physician “intravitreally administer”, to said patient, an effective amount of afibercept which is 2 mg approximately every 4 weeks for the first 5 injections.” It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to intravitreally administer an effective amount of Eylea® (afibercept) which is 2 mg approximately every 4 weeks for the first five injections in order to treat patients with diabetic retinopathy.

485. Specifically, the Eylea® label instructs physicians to treat diabetic retinopathy by administering 2 mg of Eylea® (afibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”³⁸⁴ This instruction directs physicians to treat diabetic retinopathy by administering five doses of Eylea® each approximately four weeks after the preceding dose, before transitioning to dosing every 8 weeks. Thus, the Eylea® label instructs physicians to “intravitreally administer an effective amount of afibercept which is 2 mg approximately every 4 weeks for the first 5 injections.”³⁸⁵

³⁸⁴ Eylea® Label (2022) at 1-2.

³⁸⁵ Eylea® Label (2022) at 1-2.

486. A physician practicing the dosing regimen instructed by Eylea's® label for the treatment of diabetic retinopathy would meet this limitation of claim 18, and a physician administering YESAFILI™ in the same manner would also meet this limitation.

487. Further, Mylan's proposed labeling for YESAFILI™ instructs physicians to treat diabetic retinopathy by administering 2 mg of YESAFILI™ (aflibercept-jbv) "by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)."³⁸⁶ This instruction directs physicians to treat diabetic retinopathy by administering five doses of YESAFILI™ (aflibercept-jbv) each approximately four weeks after the preceding dose, before transitioning to dosing every 8 weeks. Thus, the YESAFILI™ label instructs physicians to "intravitreally administer an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections."³⁸⁷

488. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform limitation (18a). In other words, if Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will administer YESAFILI™ to treat diabetic retinopathy by administering an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections.

489. Mylan's proposed labeling encourages, recommends, and promotes performance of limitation (18a) by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will administer YESAFILI™ to treat diabetic retinopathy by

³⁸⁶ MYL-AFL-BLA1079688 at -1079688 to -1089689.

³⁸⁷ MYL-AFL-BLA1079688 at -1079688 to -1089689.

administering an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections.

490. I incorporate by reference my analysis of this limitation in the claim charts appended hereto as Appendix D as though set forth fully herein.

3) (18b) followed by 2 mg approximately once every 8 weeks or once every 2 months.

491. Limitation (18b) requires that the physician follow step (18a) by administering, to the patient in need of treatment for diabetic retinopathy, “2 mg [aflibercept] approximately once every 8 weeks or once every 2 months.” It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to follow the first five injections of Eylea® with 2 mg Eylea® approximately once every 8 weeks or once every 2 months in order to treat patients with diabetic retinopathy.

492. Specifically, the Eylea® label instructs physicians to treat diabetic retinopathy by administering 2 mg of Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”³⁸⁸ This instruction directs physicians to administer 2mg Eylea® (aflibercept) approximately once every 8 weeks or once every 2 months, after delivering five monthly of 2 mg Eylea® (aflibercept), in order to treat diabetic retinopathy. The Eylea® label therefore instructs physicians to administer “2 mg [aflibercept] approximately once every 8 weeks or once every 2 months” in order to treat diabetic retinopathy.

³⁸⁸ Eylea® Label (2022) at 1-2.

493. A physician practicing the dosing regimen instructed by Eylea's® label for the treatment of diabetic retinopathy would meet this limitation of claim 18, and physician administering YESAFILI™ in the same manner would also meet this limitation.

494. Further, Mylan's proposed labeling for YESAFILI™ instructs physicians to treat diabetic retinopathy by administering 2 mg of YESAFILI™ (aflibercept-jbvf) "by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)."³⁸⁹ This instruction directs physicians to administer 2mg YESAFILI™ (aflibercept-jbvf) approximately once every 8 weeks or once every 2 months, after delivering five injections of 2 mg YESAFILI™ (aflibercept-jbvf), in order to treat diabetic retinopathy. The YESAFILI™ label therefore instructs physicians to administer "2 mg [aflibercept] approximately once every 8 weeks or once every 2 months" in order to treat diabetic retinopathy.³⁹⁰

495. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform limitation (18b). In other words, if Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will administer 2 mg YESAFILI™ approximately once every 8 weeks or once every 2 months (after having administered 5 injections of YESAFILI™), in order to treat diabetic retinopathy.

496. Mylan's proposed labeling encourages, recommends, and promotes performance of limitation (18b) by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will administer 2 mg YESAFILI™ approximately once every 8

³⁸⁹ MYL-AFL-BLA1079688 at -1079688 to -1089689.

³⁹⁰ MYL-AFL-BLA1079688 at -1079688 to -1089689.

weeks or once every 2 months (after having administered five injections of YESAFILITM), in order to treat diabetic retinopathy.

497. I incorporate by reference my analysis of this limitation in the claim charts appended hereto as Appendix D as though set forth fully herein

4) Claim 18 Conclusion

498. For the reasons explained above, if Mylan markets YESAFILITM according to its proposed labeling, physicians will in fact perform the method of Claim 18.

499. By marketing YESAFILITM according to its approved labeling, which instructs clinicians to use YESAFILITM in the same manner as Eylea® and in the manner recited in claim 18, Mylan specifically intends such infringement to occur and knows such infringement will occur. Mylan therefore induces infringement of claim 18 of the '601 patent.

b) Claim 19 Analysis

500. Claim 19 recites:

19. The method of claim 18, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

501. As described above, Mylan's marketing of YESAFILITM in accordance with its proposed labeling will induce infringement of claim 18 of the '601 patent. I incorporate the analysis of claim 18 as though fully set forth herein.

502. In addition, Mylan's marketing of YESAFILITM will induce physicians to perform the method of claim 18 *and* the further limitation of claim 19, "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly." It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to administer an effective amount of Eylea® (aflibercept) which is 2 mg approximately every month for the first five injections in order to treat patients with diabetic retinopathy.

503. Specifically, the Eylea® label instructs physicians to treat diabetic retinopathy by administering 2 mg of Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”³⁹¹ This instruction directs physicians to treat diabetic retinopathy by administering five injections of 2 mg Eylea® approximately monthly.³⁹² The Eylea® label therefore instructs physicians to administer an effective amount of aflibercept which is 2 mg approximately monthly.

504. A physician practicing the dosing regimen instructed by Eylea’s® label for the treatment of diabetic retinopathy would meet this limitation of claim 19, and a physician administering YESAFILI™ in the same manner would also meet this limitation.

505. Further, Mylan’s proposed labeling for YESAFILI™ instructs physicians to treat diabetic retinopathy by administering 2 mg of YESAFILI™ (aflibercept-jbv) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”³⁹³ This instruction directs physicians to treat diabetic retinopathy by administering five doses of 2 mg YESAFILI™ (aflibercept-jbv) approximately monthly.³⁹⁴ The YESAFILI™ label therefore instructs physicians to administer an effective amount of aflibercept which is 2 mg approximately monthly for the first five injections to treat diabetic retinopathy.

³⁹¹ Eylea® Label (2022) at 1-2.

³⁹² Eylea® Label (2022) at 1-2.

³⁹³ Eylea® Label (2022) at 1-2.

³⁹⁴ Eylea® Label (2022) at 1-2.

506. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform the method of claim 19.

507. Mylan's proposed labeling encourages, recommends, and promotes performance of the method of claim 19 by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 19 to treat diabetic retinopathy, and specifically intends this infringing activity.

508. I incorporate by reference my analysis of claim 19 in the claim charts appended hereto as Appendix D as though set forth fully herein.

14. Claim 21

509. Claim 21 recites:

21. The method of claim 18, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

510. I understand that claim 21 depends from claim 18. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 18 of the '601 patent. I incorporate the analysis of claim 18 as though fully set forth herein.

511. Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce physicians to perform the method of claim 18 *and* the further limitation of claim 21, "further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks."

512. By administering YESAFILI™ according to the method of claim 18, a physician administers 2 mg aflibercept for the first 5 injections—*i.e.*, injections at baseline (week 0), and weeks 4, 8, 12, and 16; the physician then follows with a 2 mg dose at approximately 8 weeks

thereafter (*i.e.*, after week 24). Claim 21 requires that the physician then revert to monthly dosing, and administer doses of aflibercept at approximately week 28 and week 32.

513. YESAFILI™'s proposed labeling recommends, encourages, and promotes such conduct in certain patients under certain circumstances—specifically, the label states that for the treatment of DR, “[s]ome patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).” As a result of this statement, some doctors will observe the need for every 4 week (monthly) dosing after week 20, and will actually perform such dosing, in accordance with claim 21. Accordingly, Mylan induces infringement of claim 21 of the '601 patent.

514. I incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix D as though set forth fully herein.

15. Claim 23

515. Claim 23 recites:

23. The method of claim 18 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

516. I understand that claim 23 depends from claim 18. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 18 of the '601 patent. I incorporate the analysis of claim 18 as though fully set forth herein.

517. Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 18 *and* the further limitation of claim 23, “wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.”

518. The POSA would understand Claim 23 to require a physician perform the method of claim 18, and then measure a gain of at least 15 letters of BCVA score. For the reasons I

explained in Section VI.D.3.e and incorporate herein by reference, this limitation requires a physician to perform the active step of measuring a gain of at least 15 letters of BCVA score.

519. Furthermore, when physicians measure visual acuity gains in patients with angiogenic disorders like diabetic retinopathy, they measure BCVA, for all the reasons I explained above in Section VI.D.4.a. I incorporate that analysis by reference herein.

520. Mylan's proposed labeling instructs doctors to use YESAFILI™ in the same way they would use Eylea®, and that YESAFILI™ is clinically equivalent to Eylea® when used according to its label.³⁹⁵ I have treated patients with diabetic retinopathy using Eylea® in my own clinical practice, by intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections, followed by 2 mg approximately once every 8 weeks or once every 2 months. I measure the BCVA of such patients before every injection, and I have measured gains of at least 15 letters of Best Corrected Visual Acuity (BCVA) score in some of these patients. I also frequently speak with other retinal specialists, and these conversations confirm that other physicians have done the same. On this basis, in combination with Mylan's instruction to doctors that YESAFILI™ is clinically equivalent to Eylea®, I conclude that if Mylan markets YESAFILI™ according to its proposed labeling, doctors will in fact perform the method of claim 18 in order to treat DR, *and* measure BCVA gains according to ETDRS letter score, as required by claim 23.

521. In light of all of the above, Mylan recommends, encourages, and promotes infringement of claim 23 of the '601 patent by recommending, encouraging, and promoting a method of treating DME using YESAFILI™ that meets every limitation of claim 23. If Mylan markets YESAFILI™ with its proposed labeling, physicians will perform acts of direct

³⁹⁵ *Supra* section VI.D.2.

infringement by treating DME using YESAFILI™ in a manner that meets every limitation of claim 23. Accordingly, the marketing of YESAFILI™ pursuant to Mylan's proposed labeling will induce infringement of claim 23 of the '601 patent.

522. I incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix D as though set forth fully herein.

16. Claim 24

523. Claim 24 Recites

24. The method of claim 23 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

524. I understand that claim 24 depends from claim 23, which in turn depends from claim 18. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 23 of the '601 patent. I incorporate that analysis of claim 23 as though fully set forth herein.

525. In addition, Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 23 *and* the further limitation of claim 24, "wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score."

a) Mylan Induces Literal Infringement of Claim 24 Under the Correct Construction of Claim 24

526. For the reasons I explained above in connection with Claim 2 of the '572 Patent, claim 24 does not require that a physician measure a gain of 15 letters in a patient using an

ETDRS chart or ETDRS protocol.³⁹⁶ I incorporate that analysis by reference as though set forth herein.

527. I described above my clinical experience measuring letter gains of at least 15 letters in patients I treat for DR using Eylea®.³⁹⁷ These are 15 letters according to ETDRS letter score, whether I measure the gain using a Snellen chart and convert the measurement to ETDRS letter scores, or whether I measure the gain using an ETDRS chart—regardless, the gain I measure is quantifiable as a gain of 15 letters according to ETDRS letter score.³⁹⁸

b) Mylan Induces Literal Infringement of Claim 24 Even If Claim 24 Requires Measurement Using the ETDRS Chart

528. Even assuming, *arguendo*, that claim 24 requires physicians to measure a 15 letter gain and to *perform that measurement using an ETDRS chart* (and to be clear, I disagree that the POSA would understand claim 24 in that way)—it is still my opinion that Mylan’s marketing of YESAFILI™ according to its proposed labeling will induce literal infringement of claim 24. Simply put, some physicians perform BCVA measurements using ETDRS *charts* to measure BCVA in their clinical practice. I have done so myself, and I am aware of colleagues who have done the same. If Mylan markets YESAFILI™ in accordance with its proposed labeling, which recommends, encourages, and promotes use of the method of claim 24, some physicians will in fact measure 15 letter gains in BCVA using an ETDRS chart. Mylan recommends, encourages, and promotes this result by virtue of its proposed labeling for YESAFILI™ and its knowledge of clinical practice.

³⁹⁶ *Supra* Section VI.D.4.b.1.

³⁹⁷ *Supra* Section VI.E.13.

³⁹⁸ *Supra* Section VI.E.13; Section VI.D.4.b.1.

c) Mylan Induces Infringement of Claim 24 Under the Doctrine of Equivalents Even If Claim 24 Requires Measurement Using the ETDRS Chart or Using an ETDRS Protocol

529. Alternatively, Mylan's marketing of YESAFILI™ according to its proposed labeling will induce infringement of claim 24 under the doctrine of equivalents even if claim 24 is interpreted to require physicians measure BCVA gains using an ETDRS chart or a more detailed ETDRS protocol. The physician measures the same visual acuity gain regardless of which chart or protocol the physician uses, and may freely convert between Snellen and ETDRS letter score results. Moreover, measuring BCVA using a Snellen chart performs substantially the same function (*i.e.*, measuring the patient's response to treatment in terms of BCVA), in substantially the same way (*i.e.*, using an eye chart and refractive lenses), to achieve substantially the same result (*i.e.*, a measurement of the patient's BCVA that can be used to make treatment decisions) as measuring BCVA using an ETDRS chart or an ETDRS protocol. This is evidenced by the fact that physicians freely convert between Snellen and ETDRS values, as I have described above.

d) Claim 24 Conclusion

530. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform the method of claim 24.

531. Mylan's proposed labeling encourages, recommends, and promotes performance of the method of claim 24 by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 24, and specifically intends this infringing activity. Mylan therefore induces infringement of claim 24.

532. I also incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix D as though set forth fully herein.

17. Claim 25

533. Claim 25 recites:

25. The method of claim 18 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

534. I understand that claim 25 depends from claim 18. The POSA would understand the method of claim 25 to require that a doctor perform a method of treating diabetic retinopathy in a patient in need thereof comprising:

- (25a) Assessing the patient for active intraocular inflammation or active ocular or periocular infection
- (25b) If the assessment determines the patient does not have the assessed-for condition, performing the method of claim 18.

535. As I described above in Section VI.E.12.a, if Mylan markets YESAFILI™ in accordance with its proposed label, physicians will perform the method of claim 18. I incorporate the analysis of claim 18 as though set forth herein.

536. In addition, if Mylan markets YESAFILI™ in accordance with its proposed label, physicians will perform the method of *first* assessing the patient for active intraocular inflammation, *then* assessing the patient for active ocular or periocular infection, and *then, if the assessment determines that the patient does not have active intraocular inflammation or active ocular or periocular infection*, performing the method of claim 18.

537. It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to assess patients for active intraocular inflammation or active ocular or periocular infection, and then, on the basis of that assessment, administer Eylea® in accordance with claim 18.³⁹⁹

³⁹⁹ Eylea® Label (2022) at 4.

538. Specifically, the Eylea® label lists both “ocular or periocular infection” and “active intraocular inflammation” as contraindications for administration of Eylea®. As the POSA would understand, when a drug label lists conditions under the heading “Contraindications,” that label instructs physicians to assess patients for the presence of the contraindicated condition and to decline to treat patients with the drug that is the subject of the label if that assessment reveals the presence of the contraindicated condition. Accordingly, the Eylea® label instructs physicians to assess patients for active intraocular inflammation and active ocular or periocular infection before administering Eylea®. A physician administering YESAFILI™ in the same manner would meet this limitation.⁴⁰⁰

539. Further, Mylan’s proposed YESAFILI™ labeling instructs physicians to assess and adhere to the same contraindications as Eylea’s® label.⁴⁰¹ Specifically, the YESAFILI™ label lists both “ocular or periocular infection” and “active intraocular inflammation” as contraindications for administration of YESAFILI™.

540. Accordingly, the YESAFILI™ label instructs physicians to assess patients for active intraocular inflammation and active ocular or periocular infection before administering YESAFILI™. In this manner, the YESAFILI™ labeling expressly directs physicians to perform the method of claim 25.

541. Thus, by marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 18 and the additional step of claim 25,

⁴⁰⁰ Eylea® Label (2022) at 4.

⁴⁰¹ MYL-AFL-BLA1079688 at Highlights of Prescribing Information (listing as contraindications “Ocular or periocular infection” and “Active intraocular inflammation”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.1 (“YESAFILI is contraindicated in patients with ocular or periocular infections.”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.2 (“YESAFILI is contraindicated in patients with active intraocular inflammation.”).

“wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.” Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 18 and the additional step of claim 25, “wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection”, and specifically intends this infringing activity. Mylan therefore induces infringement of claim 25.

542. I also incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix D as though set forth fully herein.

18. Claim 27

543. Claim 27 recites:

27. The method of claim 26, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

544. I understand that claim 27 depends from claim 26. I understand from counsel that dependent claims incorporate the limitations of the claim or claims from which they depend.

Claim 26 recites:

26. A method for treating diabetic retinopathy in a patient with diabetic macular edema, who is in need of such treatment, comprising intravitreally administering, to said patient, an effective amount of afibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or 2 months.

545. I am informed that Regeneron is not asserting claim 26 in this litigation, but I nonetheless demonstrate below that if Mylan markets YESAFILI™ in accordance with its proposed labeling, physicians will perform the method of claim 26, and Mylan directly recommends, encourages, and promotes this result by virtue of its proposed labeling and other conduct.

a) Unasserted Claim 26

546. Claim 26 contains three limitations, as follows:

- (26pre) A method for treating diabetic retinopathy in a patient with diabetic macular edema, who is in need of such treatment, comprising
 - (26a) intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections,
 - (26b) followed by 2 mg approximately once every 8 weeks or 2 months.

547. By marketing YESAFILI™ in accordance with its proposed labeling, Mylan knows and specifically intends that physicians will perform every limitation of the method of claim 26. I explain the basis for my opinion in further detail below, and in the claim charts appended to this report at Appendix D. I hereby incorporate by reference my analysis in those claim charts as though set forth fully herein.

1) (26pre) A method for treating diabetic retinopathy in a patient with diabetic macular edema, who is in need of such treatment, comprising

548. With respect to the first limitation (also called the preamble)—“A method for treating diabetic retinopathy in a patient with diabetic macular edema, who is in need of such treatment, comprising”—it is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to administer Eylea® to treat diabetic retinopathy in a patient with diabetic macular edema, who is in need of such treatment.⁴⁰² Specifically, the Eylea® label instructs physicians to administer aflibercept to treat “Diabetic Macular Edema (DME) and Diabetic Retinopathy

⁴⁰² Eylea® Label (2022) at 1-2.

(DR)," which includes the treatment of DR in patients with DME.⁴⁰³ As I explained above, DME is a complication of DR.⁴⁰⁴

549. Further, Mylan's proposed YESAFILITM labeling instructs physicians to administer YESAFILITM to treat DR in patients with DME.⁴⁰⁵ Specifically, Mylan's proposed labeling for YESAFILITM expressly instructs physicians to administer YESAFILITM to treat "Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)," which includes DR in patients with DME.⁴⁰⁶

550. If Mylan markets YESAFILITM accompanied by its proposed labeling, one or more physicians will perform limitation (26pre). In other words, if Mylan markets YESAFILITM accompanied by its proposed labeling, one or more physicians will administer YESAFILITM to treat DR in patients with DME.

551. Mylan's proposed labeling encourages, recommends, and promotes performance of limitation (26pre) by physicians. Indeed, by marketing YESAFILITM with its proposed labeling, Mylan knows that physicians will administer YESAFILITM to treat DR in patients with DME consistent with Claim 26 of the '601 Patent, and specifically intends this infringing activity.

⁴⁰³ Eylea® Label (2022) at 1-2.

⁴⁰⁴ *Supra* Section IV.A.2 and Section IV.A.3.

⁴⁰⁵ MYL-AFL-BLA1079688 at -1079688 to -1089689.

⁴⁰⁶ MYL-AFL-BLA1079688 at -1079688 to -1089689.

552. I incorporate by reference my analysis of this limitation in the claim charts appended hereto as Appendix D as though set forth fully herein.

- 2) (26a) intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections,

553. Limitation (26a) requires that the physician “intravitreally administer[], to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections.” It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to intravitreally administer an effective amount of Eylea® (aflibercept) which is 2 mg approximately every 4 weeks for the first five injections in order to treat DR in patients with DME.

554. Specifically, the Eylea® label instructs physicians to treat diabetic retinopathy in patients with DME by administering 2 mg of Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”⁴⁰⁷ This instruction directs physicians to treat DR in patients with DME by administering five doses of Eylea® each approximately four weeks after the preceding dose, before transitioning to dosing every 8 weeks. Thus, the Eylea® label instructs physicians to “intravitreally administer[] an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections.”⁴⁰⁸

⁴⁰⁷ Eylea® Label (2022) at 1-2.

⁴⁰⁸ Eylea® Label (2022) at 1-2.

555. A physician practicing the dosing regimen instructed by Eylea's® label for the treatment DR in patients with DME would meet this limitation of claim 26, and a physician administering YESAFILI™ in the same manner would also meet this limitation.

556. Further, Mylan's proposed labeling for YESAFILI™ instructs physicians to treat DR in patients with DME by administering 2 mg of YESAFILI™ (aflibercept-jbvf) "by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)."⁴⁰⁹ This instruction directs physicians to treat DR in patients with DME by administering five doses of YESAFILI™ (aflibercept-jbvf) each approximately four weeks after the preceding dose, before transitioning to dosing every 8 weeks. Thus, the YESAFILI™ label instructs physicians to "intravitreally administer[] an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections."⁴¹⁰

557. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform limitation (26a). In other words, if Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will administer YESAFILI™ to treat DR in patients with DME by administering an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections.

558. Mylan's proposed labeling encourages, recommends, and promotes performance of limitation (26a) by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will administer YESAFILI™ to treat DR in patients with DME by

⁴⁰⁹ MYL-AFL-BLA1079688 at -1079688 to -1089689.

⁴¹⁰ MYL-AFL-BLA1079688 at -1079688 to -1089689.

administering an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections.

559. I incorporate by reference my analysis of this limitation in the claim charts appended hereto as Appendix D as though set forth fully herein.

3) (26b) followed by 2 mg approximately once every 8 weeks or once every 2 months.

560. Limitation (26b) requires that the physician follow step (26a) by administering “2 mg [aflibercept] approximately once every 8 weeks or once every 2 months” in order to treat diabetic retinopathy in a patient with diabetic macular edema, who is in need of such treatment. It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to follow the first five injections of Eylea® with 2 mg Eylea® approximately once every 8 weeks or once every 2 months in order to treat DR in patients with DME.

561. Specifically, the Eylea® label instructs physicians to treat DR in patients with DME by administering 2 mg of Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”⁴¹¹ This instruction directs physicians to administer 2mg Eylea® (aflibercept) approximately once every 8 weeks or once every 2 months, after delivering five monthly injections of 2 mg Eylea® (aflibercept), in order to treat DR in patients with DME. The Eylea® label therefore instructs physicians to administer “2 mg [aflibercept] approximately once every 8 weeks or once every 2 months” in order to treat DR in patients with DME.

⁴¹¹ Eylea® Label (2022) at 1-2.

562. A physician practicing the dosing regimen instructed by Eylea's® label for the treatment of DR in patients with DME would meet this limitation of claim 26, and a physician administering YESAFILI™ in the same manner would also meet this limitation.

563. Further, Mylan's proposed labeling for YESAFILI™ instructs physicians to treat DR in patients with DME by administering 2 mg of YESAFILI™ (afibercept-jbvf) "by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)."⁴¹² This instruction directs physicians to administer 2mg YESAFILI™ (afibercept-jbvf) approximately once every 8 weeks or once every 2 months, after delivering five monthly doses of 2 mg YESAFILI™ (afibercept-jbvf), in order to treat DR in patients with DME. Thus, the YESAFILI™ label instructs physicians to administer (afibercept-jbvf) approximately once every 8 weeks or 2 months, after administering five injections of 2 mg YESAFILI™ (afibercept-jbvf). The YESAFILI™ label therefore instructs physicians to administer "2 mg [afibercept] approximately once every 8 weeks or once every 2 months" in order to treat DR in patients with DME.^{4¹³}

564. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform limitation (26b). In other words, if Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will administer 2 mg YESAFILI™ approximately once every 8 weeks or once every 2 months (after having administered five injections of YESAFILI™), in order to treat DR in patients with DME.

^{4¹²} MYL-AFL-BLA1079688 at -1079688 to -1089689.

^{4¹³} MYL-AFL-BLA1079688 at -1079688 to -1089689.

565. Mylan's proposed labeling encourages, recommends, and promotes performance of limitation (26b) by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will administer 2 mg YESAFILI™ approximately once every 8 weeks or once every 2 months (after having administered five injections of YESAFILI™), in order to treat DR in patients with DME.

566. I incorporate by reference my analysis of this limitation in the claim charts appended hereto as Appendix D as though set forth fully herein

4) Claim 26 Conclusion

567. For the reasons explained above, if Mylan markets YESAFILI™ according to its proposed labeling, physicians will in fact perform the method of Claim 26.

568. By marketing YESAFILI™ according to its approved labeling, which instructs clinicians to use YESAFILI™ in the same manner as Eylea® and in the manner recited in claim 26, Mylan specifically intends such infringement to occur and knows such infringement will occur. Mylan therefore induces infringement of claim 26 of the '601 patent.

b) Claim 27 Analysis

569. Claim 27 recites:

27. The method of claim 26, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

570. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 26 of the '601 patent. I incorporate the analysis of claim 26 as though fully set forth herein.

571. Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 26 *and* the further limitation of claim 27, "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly." It is a standard Eylea®

clinical practice, as exemplified by the Eylea® label, to administer an effective amount of Eylea® (aflibercept) which is 2 mg approximately every month for the first five injections in order to treat DR in patients with DME.

572. Specifically, the Eylea® label instructs physicians to treat DR in patients with DME by administering 2 mg of Eylea® (aflibercept) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”⁴¹⁴ This instruction directs physicians to treat DR in patients with DME by administering five injections of 2 mg Eylea® approximately monthly.⁴¹⁵ The Eylea® label therefore instructs physicians to administer an effective amount of aflibercept which is 2 mg approximately monthly.

573. A physician practicing the dosing regimen instructed by Eylea’s® label for the treatment of DR in patients with DME would meet this limitation of claim 27, and physician administering YESAFILI™ in the same manner would also meet this limitation.

574. Further, Mylan’s proposed labeling for YESAFILI™ instructs physicians treat DR in patients with DME by administering 2 mg of YESAFILI™ (aflibercept-jbvf) “by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”⁴¹⁶ This instruction directs physicians to treat DR in patients with DME by administering five doses of 2 mg YESAFILI™ (aflibercept-jbvf) approximately monthly.⁴¹⁷ The

⁴¹⁴ Eylea® Label (2022) at 1-2.

⁴¹⁵ Eylea® Label (2022) at 1-2.

⁴¹⁶ Eylea® Label (2022) at 1-2.

⁴¹⁷ Eylea® Label (2022) at 1-2.

YESAFILI™ label therefore instructs physicians to administer an effective amount of aflibercept which is 2 mg approximately monthly for the first five injections to treat DR in patients with DME.

575. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform the method of claim 27.

576. Mylan's proposed labeling encourages, recommends, and promotes performance of the method of claim 27 by physicians. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 27 to treat DR in patients with DME, and specifically intends this infringing activity.

577. I incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix D as though set forth fully herein.

19. Claim 28

578. Claim 28 recites:

12. The method of claim 26, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

579. I understand that claim 28 depends from claim 26. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 26 of the '601 patent. I incorporate the analysis of claim 26 as though fully set forth herein.

580. Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce physicians to perform the method of claim 26 *and* the further limitation of claim 28, "further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks."

581. By administering YESAFILI™ according to the method of claim 26, a physician administers 2 mg aflibercept for the first 5 injections—i.e., injections at baseline (week 0), and weeks 4, 8, 12, and 16; the physician then follows with a 2 mg dose at approximately 8 weeks thereafter (i.e., after week 24). Claim 28 requires that the physician then revert to monthly dosing, and administer doses of aflibercept at approximately week 28 and week 32.

582. YESAFILI™'s proposed labeling recommends, encourages, and promotes such conduct in certain patients under certain circumstances—specifically, the label states that for the treatment DR in patients with DME, “[s]ome patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).” As a result of this statement, some doctors will observe the need for every 4 week (monthly) dosing after week 20, and will actually perform such dosing, in accordance with claim 28. Accordingly, Mylan induces infringement of claim 28 of the '601 patent.

583. I incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix D as though set forth fully herein.

20. Claim 31

584. Claim 31 recites:

31. The method of claim 26 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

585. I understand that claim 31 depends from claim 26. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 26 of the '601 patent. I incorporate the analysis of claim 26 as though fully set forth herein.

586. Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 26 *and* the further limitation of claim 31, "wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score."

587. The POSA would understand Claim 31 to require a physician perform the method of claim 26, and then measure a gain of at least 15 letters of BCVA score. For the reasons I explained in Section VI.D.3.e and incorporate herein by reference, this limitation requires a physician to perform the active step of measuring a gain of at least 15 letters of BCVA score.

588. Furthermore, when physicians measure visual acuity gains in patients with angiogenic disorders like DR in patients with DME, they measure BCVA, for all the reasons I explained above in Section VI.D.4.a. I incorporate that analysis by reference herein.

589. Mylan's proposed labeling instructs doctors to use YESAFILI™ in the same way they would use Eylea®, and that YESAFILI™ is clinically equivalent to Eylea® when used according to its label.⁴¹⁸ I have treated DR in patients with DME using Eylea® in my own clinical practice, by intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections, followed by 2 mg approximately once every 8 weeks or once every 2 months. I measure the BCVA of such patients before every injection, and I have measured gains of at least 15 letters of Best Corrected Visual Acuity (BCVA) score in some of these patients. I also frequently speak with other retinal specialists, and these conversations confirm that other physicians have done the same. On this basis, in combination with Mylan's instruction to doctors that YESAFILI™ is clinically equivalent to Eylea®, I conclude that if Mylan markets YESAFILI™ according to its proposed labeling, doctors will in fact perform the method of claim 26 in order to treat DR in patients with

⁴¹⁸ *Supra* section VI.D.2.

DME, *and* measure gains of at least 15 letters of Best Corrected Visual Acuity (BCVA), as required by claim 31.

590. In light of all of the above, Mylan recommends, encourages, and promotes infringement of claim 31 of the '601 patent by recommending, encouraging, and promoting a method of treating DME using YESAFILI™ that meets every limitation of claim 31. If Mylan markets YESAFILI™ with its proposed labeling, physicians will perform acts of direct infringement by treating DME using YESAFILI™ in a manner that meets every limitation of claim 31. Accordingly, the marketing of YESAFILI™ pursuant to Mylan's proposed labeling will induce infringement of claim 31 of the '601 patent.

591. I incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix D as though set forth fully herein.

21. Claim 32

592. Claim 32 recites:

32. The method of claim 31 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

593. I understand that claim 32 depends from claim 31, which in turn depends from claim 26. As described above, Mylan's marketing of YESAFILI™ in accordance with its proposed labeling will induce infringement of claim 31 of the '601 patent. I incorporate the analysis of claim 31 as though fully set forth herein.

594. Mylan's marketing of YESAFILI™ will induce physicians to perform the method of claim 31 *and* the further limitation of claim 32, "wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score."

a) Mylan Induces Literal Infringement of Claim 32 Under the Correct Construction of Claim 32

595. For the reasons I explained above in connection with Claim 2 of the '572 Patent, claim 32 does not require that a physician measure a gain of 15 letters in a patient using an ETDRS chart or ETDRS protocol.⁴¹⁹ I incorporate that analysis by reference as though set forth herein.

596. I described above my clinical experience measuring letter gains of at least 15 letters when I have treated DR in patients with DME using Eylea®.⁴²⁰ When I measure 15 letter gains in such patients, these are 15 letters according to ETDRS letter score. This is true whether I measure the gain using a Snellen chart and convert the measurement to ETDRS letter scores, or whether I measure the gain using an ETDRS chart—regardless, the gain I measure is quantifiable as a gain of 15 letters according to ETDRS letter score.⁴²¹

b) Mylan Induces Literal Infringement of Claim 32 Even If Claim 32 Requires Measurement Using the ETDRS Chart

597. Even assuming, *arguendo*, that claim 32 requires physicians to measure a 15 letter gain and to *perform that measurement using an ETDRS chart* (and to be clear, I disagree that the POSA would understand claim 32 in that way)—it is still my opinion that Mylan's marketing of YESAFILI™ according to its proposed labeling will induce literal infringement of claim 32. Simply put, some physicians perform BCVA measurements using ETDRS charts to measure BCVA in their clinical practice. I have done so myself, and I am aware of colleagues who have done the same. If Mylan markets YESAFILI™ in accordance with its proposed labeling, which

⁴¹⁹ *Supra* Section VI.D.4.b.1.

⁴²⁰ *Supra* Section VI.E.13.

⁴²¹ *Supra* Section VI.E.13; Section VI.D.4.b.1.

recommends, encourages, and promotes use of the method of claim 32, some physicians will in fact measure 15 letter gains in BCVA using an ETDRS chart. Mylan recommends, encourages, and promotes this result by virtue of its proposed labeling for YESAFILI™ and its knowledge of clinical practice.

c) Mylan Induces Infringement of Claim 32 Under the Doctrine of Equivalents Even If Claim 32 Requires Measurement Using the ETDRS Chart or Using an ETDRS Protocol

598. Alternatively, Mylan's marketing of YESAFILI™ according to its proposed labeling will induce infringement of claim 32 under the doctrine of equivalents even if claim 32 is interpreted to require physicians measure BCVA gains using an ETDRS chart or a more detailed ETDRS protocol. The physician measures the same visual acuity gain regardless of which chart or protocol the physician uses, and may freely convert between Snellen and ETDRS letter score results. Moreover, measuring BCVA using a Snellen chart performs substantially the same function (*i.e.*, measuring the patient's response to treatment in terms of BCVA), in substantially the same way (*i.e.*, using an eye chart and refractive lenses), to achieve substantially the same result (*i.e.*, a measurement of the patient's BCVA that can be used to make treatment decisions) as measuring BCVA using an ETDRS chart or an ETDRS protocol. This is evidenced by the fact that physicians freely convert between Snellen and ETDRS values, as I have described above.

d) Claim 32 Conclusion

599. If Mylan markets YESAFILI™ accompanied by its proposed labeling, one or more physicians will perform the method of claim 32.

600. Mylan's proposed labeling encourages, recommends, and promotes performance of the method of claim 32 by physicians. Indeed, by marketing YESAFILI™ with its proposed

labeling, Mylan knows that physicians will perform the method of claim 32, and specifically intends this infringing activity. Mylan therefore induces infringement of claim 32.

601. I also incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix D as though set forth fully herein

22. Claim 33

602. Claim 33 recites:

33. The method of claim 26 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

603. I understand that claim 33 depends from claim 26. The POSA would understand the method of claim 33 to require that a doctor diabetic retinopathy in a patient with diabetic macular edema, who is in need of such treatment, comprising:

- (33a) Assessing the patient for active intraocular inflammation or active ocular or periocular infection
- (33b) If the doctor determines the patient does not have the assessed-for condition, performing the method of claim 26.

604. As I described above in Section VI.E.16.a, if Mylan markets YESAFILI™ in accordance with its proposed label, physicians will perform the method of claim 26. I incorporate the analysis of claim 26 as though set forth herein.

605. In addition, if Mylan markets YESAFILI™ in accordance with its proposed label, physicians will perform the method of *first* assessing the patient for active intraocular inflammation, *then* assessing the patient for active ocular or periocular infection, and *then, if the assessment determines the patient does not have active intraocular inflammation or active ocular or periocular infection*, performing the method of claim 26.

606. It is a standard Eylea® clinical practice, as exemplified by the Eylea® label, to assess patients for active intraocular inflammation or active ocular or periocular infection, and then, on the basis of that assessment, administer Eylea® in accordance with claim 26.⁴²²

607. Specifically, the Eylea® label lists both “ocular or periocular infection” and “active intraocular inflammation” as contraindications for administration of Eylea®. As the POSA would understand, when a drug label lists conditions under the heading “Contraindications,” that label instructs physicians to assess patients for the presence of the contraindicated condition and to decline to treat patients with the drug that is the subject of the label if that assessment reveals the presence of the contraindicated condition. Accordingly, the Eylea® label instructs physicians to assess patients for active intraocular inflammation and active ocular or periocular infection before administering Eylea®. A physician administering YESAFILI™ in the same manner would meet this limitation.⁴²³

608. Further, Mylan’s proposed YESAFILI™ labeling instructs physicians to assess and adhere to the same contraindications as Eylea’s® label.⁴²⁴ Specifically, the YESAFILI™ label lists both “ocular or periocular infection” and “active intraocular inflammation” as contraindications for administration of YESAFILI™.

609. Accordingly, the YESAFILI™ label instructs physicians to assess patients for active intraocular inflammation and active ocular or periocular infection before administering

⁴²² Eylea® Label (2022) at 4.

⁴²³ Eylea® Label (2022) at 4.

⁴²⁴ MYL-AFL-BLA1079688 at Highlights of Prescribing Information (listing as contraindications “Ocular or periocular infection” and “Active intraocular inflammation”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.1 (“YESAFILI is contraindicated in patients with ocular or periocular infections.”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.2 (“YESAFILI is contraindicated in patients with active intraocular inflammation.”).

YESAFILI™. In this manner, the YESAFILI™ labeling expressly directs physicians to perform the method of claim 33.

610. Thus, by marketing YESAFILI™ with its proposed labeling, Mylan will cause one or more physicians to perform the method of claim 26 and the additional limitation of claim 33, "wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection," As required by claim 33. Indeed, by marketing YESAFILI™ with its proposed labeling, Mylan knows that physicians will perform the method of claim 26, and the additional limitation of claim 26, "wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection", as required by claim 33 and specifically intends this infringing activity. Mylan therefore induces infringement of claim 33.

611. I also incorporate by reference my analysis of this claim in the claim charts appended hereto as Appendix D as though set forth fully herein.



Dr. Karl Csaky
Dated: February 2, 2023

APPENDIX C

APPENDIX C

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(1pre) 1. A method of treating an angiogenic eye disorder in a patient in need thereof comprising	<p>Mylan's proposed labeling directs physicians to treat angiogenic eye disorders by administering aflibercept.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing administration of aflibercept to treat Wet AMD, RVO, DR, and DME); MYL-AFL-BLA1079688 at - 1079700, at section 12.1 (“Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PIGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PIGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PIGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.”).</p> <p>In accordance with Mylan's proposed labeling, physicians will administer aflibercept to treat angiogenic eye disorders.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing administration of aflibercept to treat Wet AMD, RVO, DR, and DME); MYL-AFL-BLA1079688 at - 1079700, at section 12.1 (“Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PIGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PIGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PIGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.”).</p>
(1a) sequentially administering to the patient by intravitreal injection a	Mylan's proposed labeling directs physicians to treat wet AMD, DME, and DR—angiogenic eye disorders—by administering a single initial dose of 2 mg of aflibercept,

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single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;	<p>followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing that, for the treatment of wet AMD, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months),” and directing that, for the treatment of DME and DR, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)”).</i></p> <p>In accordance with Mylan’s proposed labeling, physicians will treat wet AMD, DME, DR—angiogenic eye disorders—by administering a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing that, for the treatment of wet AMD, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months),” and directing that, for the treatment of DME and DR, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)”).</i></p>
(1b) wherein each secondary dose is administered approximately 4 weeks following the immediately preceding dose; and	<p>Mylan’s proposed labeling directs physicians to administer each secondary dose of 2 mg of aflibercept approximately 4 weeks following the immediately preceding dose.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing that, for the treatment of wet AMD, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL)</i></p>

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	<p>administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)," and directing that, for the treatment of DME and DR, "[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)").</p> <p>In accordance with Mylan's proposed labeling, physicians will treat angiogenic eye disorders by administering each secondary dose of 2 mg of aflibercept approximately 4 weeks following the immediately preceding dose.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing that, for the treatment of wet AMD, "[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)," and directing that, for the treatment of DME and DR, "[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)").</i></p>
(1c) wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose;	<p>Following administration of the secondary doses, as directed by Mylan's proposed labeling for the treatment of wet AMD, DME, and DR (i.e., angiogenic eye disorders), for example, Mylan's proposed labeling directs physicians to administer each tertiary dose of 2 mg (0.05 mL) of aflibercept approximately once every 8 weeks or once every 2 months to treat the angiogenic eye disorder.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at Highlights of Prescribing Information ("The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)."); MYL-AFL-BLA1079688 at - 1079689, at section 2.2 ("The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by</i></p>

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	<p>intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”); MYL-AFL-BLA1079688 at -1079689, at Section 2.4 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”); MYL-AFL-BLA1079688 at -1079690, at Section 2.5 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”)</p> <p>In accordance with Mylan’s proposed labeling, following administration of secondary doses of 2 mg of aflibercept, physicians will administer each tertiary dose of 2 mg (0.05 mL) of aflibercept approximately once every 8 weeks or once every 2 months to treat the angiogenic eye disorder.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”); MYL-AFL-BLA1079688 at -1079689, at section 2.2 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”); MYL-AFL-BLA1079688 at -1079689, at Section 2.4 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”); MYL-AFL-BLA1079688 at -1079690, at Section 2.5 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”)</p>

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(1d) wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose.	<p>Mylan's proposed labeling directs physicians to administer aflibercept to treat angiogenic eye disorders such that a patient will achieve a gain in visual acuity within 52 weeks after the initial dose.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Both aflibercept 2Q8 and aflibercept 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group in year 1.”); MYL-AFL-BLA1079688 at -1079704–1079706, at section 14.2 (“In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA compared to baseline. At week 24, the aflibercept 2 mg Q4 group was superior to the control group for the primary endpoint.”); MYL-AFL-BLA1079688 at -1079706–1079707, at section 14.3 (“In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline.”); MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4 (“In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score.”); MYL-AFL-BLA1079688 at -1079710–1079713, at section 14.5 (“The primary efficacy endpoint was the proportion of patients who improved by ≥ 2 steps on the DRSS from baseline to week 24 in the combined aflibercept groups and at week 52 in the 2Q16 and 2Q8 groups individually versus sham.”); MYL-AFL0006405; MYL-AFL0004715; Brown et al., <i>Evaluation of Intravitreal Aflibercept for the Treatment of Severe Nonproliferative Diabetic Retinopathy: Results from the Panorama Clinical Trial</i>, Jama Ophthalmol. 2021;139(9):946-655 (“Brown 2021”).</p> <p>In accordance with Mylan's proposed labeling, physicians will treat angiogenic eye disorders by administering aflibercept such that a patient will achieve a gain in visual acuity within 52 weeks after the initial dose.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52</p>

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	<p>compared to baseline. Both aflibercept 2Q8 and aflibercept 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group in year 1.”); MYL-AFL-BLA1079688 at -1079704–1079706, at section 14.2 (“In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA compared to baseline. At week 24, the aflibercept 2 mg Q4 group was superior to the control group for the primary endpoint.”); MYL-AFL-BLA1079688 at -1079706–1079707, at section 14.3 (“In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline.”); MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4 (“In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score.”); MYL-AFL-BLA1079688 at -1079710–1079713, at section 14.5 (“The primary efficacy endpoint was the proportion of patients who improved by ≥ 2 steps on the DRSS from baseline to week 24 in the combined aflibercept groups and at week 52 in the 2Q16 and 2Q8 groups individually versus sham.”); MYL-AFL0006405; MYL-AFL0004715; Brown 2021.</p>
2. The method of claim 1 wherein the patient achieves a gain in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 1 as set forth above.</p> <p>Mylan’s proposed labeling directs physicians to administer aflibercept to treat wet AMD, DME, and/or DR (i.e., angiogenic eye disorders) such that a patient will achieve a gain in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with aflibercept) in the two studies (VIEW1 and VIEW2). In each study, up to week 52, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 3 initial monthly doses (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); 3) aflibercept 0.5 mg administered</p>

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	<p>every 4 weeks (aflibercept 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4.”); MYL-AFL-BLA1079688 at -1079702–1079703, at section 14.1, tbl. 4 (showing that 31% (VIEW1 and VIEW2) of wet AMD patients treated with three monthly 2 mg doses of aflibercept followed by 2 mg doses administered once every 8 weeks gained at least 15 letters of vision (i.e., BCVA score)); MYL-AFL-BLA1079688 at -1079708–1079710, at Section 14.4; MYL-AFL0004715; MYL-AFL-BLA1079688 at -1079710–1079713, at Section 14.5.</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat angiogenic eye disorders by using the method of claim 1, resulting in a patient achieving a gain in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with aflibercept) in the two studies (VIEW1 and VIEW2). In each study, up to week 52, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 3 initial monthly doses (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); 3) aflibercept 0.5 mg administered every 4 weeks (aflibercept 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4.”); MYL-AFL-BLA1079688 at -1079702–1079703, at section 14.1, tbl. 4 (showing that 31% (VIEW1 and VIEW2) of wet AMD patients treated with three monthly 2 mg doses of aflibercept followed by 2 mg doses administered once every 8 weeks gained at least 15 letters of vision (i.e., BCVA score)); MYL-AFL-BLA1079688 at -1079708–1079710, at Section 14.4; MYL-AFL-BLA1079688 at -1079710–1079713, at Section 14.5; MYL-AFL0006405; MYL-AFL0004715; Brown 2021.</p>
3. The method of claim 2 wherein the patient gains at least 7 letters Best	Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 2 as set forth above.

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Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.	<p>Mylan's proposed labeling directs physicians to administer aflibercept to treat wet AMD such that a patient will gain at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with aflibercept) in the two studies (VIEW1 and VIEW2). In each study, up to week 52, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 3 initial monthly doses (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); 3) aflibercept 0.5 mg administered every 4 weeks (aflibercept 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4.”); MYL-AFL-BLA1079688 at -1079702–1079703, at section 14.1, tbl. 4 (showing that 31% (VIEW1 and VIEW2) of wet AMD patients treated with three monthly 2 mg doses of aflibercept followed by 2 mg doses administered once every 8 weeks gained at least 15 letters of vision (i.e., BCVA score)); MYL-AFL-BLA1079688 at -1079708–1079710, at Section 14.4; MYL-AFL-BLA1079688 at -1079710–1079713, at Section 14.5; MYL-AFL0006405; MYL-AFL0004715; Brown 2021.</i></p> <p>In accordance with Mylan's proposed labeling, physicians will treat angiogenic eye disorders by using the method of claim 2, resulting in a patient gaining at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with aflibercept) in the two studies (VIEW1 and VIEW2). In each study, up to week 52, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) aflibercept</i></p>

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	administered 2 mg every 8 weeks following 3 initial monthly doses (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); 3) aflibercept 0.5 mg administered every 4 weeks (aflibercept 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4.”); MYL-AFL-BLA1079688 at -1079702–1079703, at section 14.1, tbl. 4 (showing that 31% (VIEW1 and VIEW2) of wet AMD patients treated with three monthly 2 mg doses of aflibercept followed by 2 mg doses administered once every 8 weeks gained at least 15 letters of vision (i.e., BCVA score)); MYL-AFL-BLA1079688 at -1079708–1079710, at Section 14.4; MYL-AFL-BLA1079688 at -1079710–1079713, at Section 14.5; MYL-AFL0006405; MYL-AFL0004715; Brown 2021.
4. The method of claim 3 wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 3 as set forth above.</p> <p>Mylan’s proposed labeling directs physicians to administer aflibercept to treat angiogenic eye disorders such that a patient will achieve the gain in visual acuity within 24 weeks after the initial dose.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at -1079704–1079706, at section 14.2 (“In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA compared to baseline. At week 24, the aflibercept 2 mg Q4 group was superior to the control group for the primary endpoint.”); MYL-AFL-BLA1079688 at -1079706–1079707, at section 14.3 (“In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline.”); MYL-AFL-BLA1079688 at -1079710–1079713, at section 14.5 (“The primary efficacy endpoint was the proportion of patients who improved by ≥2 steps on the DRSS from baseline to week 24 in the combined aflibercept groups and at week 52 in the 2Q16 and 2Q8 groups individually versus sham.”); MYL-AFL-BLA1079688 at -1079702–1079704, at Section 14.1; MYL-AFL-BLA1079688 at -1079708–1079710, at Section 14.4; MYL-AFL0004715; MYL-AFL0006405; MYL-AFL0004715; Brown 2021.</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat angiogenic eye disorders by administering</p>

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	<p>aflibercept such that a patient will achieve the gain in visual acuity within 4 weeks after the initial dose.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079704–1079706, at section 14.2 (“In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA compared to baseline. At week 24, the aflibercept 2 mg Q4 group was superior to the control group for the primary endpoint.”); MYL-AFL-BLA1079688 at -1079706–1079707, at section 14.3 (“In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline.”); MYL-AFL-BLA1079688 at -1079710–1079713, at section 14.5 (“The primary efficacy endpoint was the proportion of patients who improved by ≥2 steps on the DRSS from baseline to week 24 in the combined aflibercept groups and at week 52 in the 2Q16 and 2Q8 groups individually versus sham.”); MYL-AFL-BLA1079688 at -1079702–1079704, at Section 14.1; MYL-AFL-BLA1079688 at -1079708–1079710, at Section 14.4; MYL-AFL0004715; MYL-AFL0006405; MYL-AFL0004715; Brown 2021.</i></p>
5. The method of claim 3 wherein only two secondary doses are administered to the patient.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 3 as set forth above.</p> <p>Mylan’s proposed labeling directs physicians to treat angiogenic eye disorders by administering to the patient only two secondary doses.</p> <p><i>See, e.g., MYL-AFL-BLA1079688, at Highlights of Prescribing Information (“The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months . . .”); MYL-AFL-BLA1079688 at -1079689, at section 2.2 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months) . . .”); MYL-AFL-BLA1079688 at -1079702–1079704, at Section 14.1.</i></p> <p>In accordance with Mylan’s proposed labeling, physicians will treat angiogenic eye disorders by administering to the patient only two secondary doses.</p>

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	<p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months . . .”); MYL-AFL-BLA1079688 at -1079689, at section 2.2 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months) . . .”); MYL-AFL-BLA1079688 at -1079702–1079704, at Section 14.1.</p>
6. The method of claim 3 wherein the aflibercept is formulated as an isotonic solution.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 3 as set forth above.</p> <p>Mylan’s M710 is a product biosimilar to and/or interchangeable with aflibercept that is formulated as an isotonic solution.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA0002879 at -0002881 (BLA section 3.2.P.2.2.1) (“M710 drug product (DP) has been developed as a biosimilar medicinal product of US-licensed reference product (RP) Eylea® (aflibercept), Regeneron Pharmaceuticals (RP), BLA 125387. Formulation development studies were directed towards identification of a formulation that is comparable to RP.”), <i>id.</i> at -0002887 (BLA section 3.2.P.2.2.1.2.1.2)(“The osmolality of all six formulations is close to isotonic (Table 3.2.P.2.2-11).”); <i>id.</i> at -0002903 (tbl. 3.2.P.2.2-11).</p>
7. The method of claim 3 wherein the aflibercept is formulated with a nonionic surfactant.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 3 as set forth above.</p> <p>Mylan’s M710 is a product biosimilar to and/or interchangeable with aflibercept that is formulated with a nonionic surfactant.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA0002860 at -0002867 (“M710 is an aseptically filled drug product for intravitreal injection. It is a liquid being developed as a biosimilar to EYLEA® (aflibercept) injection; MYL-AFL-BLA0002860 at -0002868 (“Histidine buffer is a pH adjuster and Polysorbate 20 a nonionic surfactant.”); MYL-AFL-BLA0013850, at -13877; MYL-AFL-BLA1080797 at -1080833 (section 3.2.S.2.2.4.2.7) (██████████ Trehalose dihydrate, ██████████ PS20, pH 6.2 and ██████████ His-HCl, pH 6.2 is added to a final concentration of ██████████</p>

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	[REDACTED] Trehalose dihydrate, [REDACTED] PS20 and [REDACTED] protein concentration.”).
8. The method of claim 2 wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 2 as set forth above.</p> <p>Mylan’s proposed labeling directs physicians to administer aflibercept to treat angiogenic eye disorders such that a patient will gain at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with aflibercept) in the two studies (VIEW1 and VIEW2). In each study, up to week 52, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 3 initial monthly doses (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); 3) aflibercept 0.5 mg administered every 4 weeks (aflibercept 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4.”); MYL-AFL-BLA1079688 at -1079702–1079703, at section 14.1, tbl. 4 (showing that 31% (VIEW1 and VIEW2) of wet AMD patients treated with three monthly 2 mg doses of aflibercept followed by 2 mg doses administered once every 8 weeks gained at least 15 letters of vision (i.e., BCVA score)); MYL-AFL-BLA1079688 at -1079708–1079710, at Section 14.4; MYL-AFL-BLA1079688 at -1079710–1079713, at Section 14.5; MYL-AFL0006405; MYL-AFL0004715; Brown 2021.</i></p> <p>In accordance with Mylan’s proposed labeling, physicians will treat angiogenic eye disorders by using the method of claim 2, resulting in a patient gaining at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“The safety and efficacy of aflibercept were</i></p>

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	assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with aflibercept) in the two studies (VIEW1 and VIEW2). In each study, up to week 52, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 3 initial monthly doses (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); 3) aflibercept 0.5 mg administered every 4 weeks (aflibercept 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4.”); MYL-AFL-BLA1079688 at -1079702–1079703, at section 14.1, tbl. 4 (showing that 31% (VIEW1 and VIEW2) of wet AMD patients treated with three monthly 2 mg doses of aflibercept followed by 2 mg doses administered once every 8 weeks gained at least 15 letters of vision (i.e., BCVA score)); MYL-AFL-BLA1079688 at -1079708–1079710, at Section 14.4; MYL-AFL-BLA1079688 at -1079710–1079713, at Section 14.5; MYL-AFL0006405; MYL-AFL0004715; Brown 2021.
9. The method of claim 8 wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 8 as set forth above.</p> <p>Mylan’s proposed labeling directs physicians to administer aflibercept to treat angiogenic eye disorders such that a patient will achieve the gain in visual acuity within 24 weeks after the initial dose.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at -1079704–1079706, at section 14.2 (“In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA compared to baseline. At week 24, the aflibercept 2 mg Q4 group was superior to the control group for the primary endpoint.”); MYL-AFL-BLA1079688 at -1079706–1079707, at section 14.3 (“In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline.”); MYL-AFL-BLA1079688 at -1079710–1079713, at section 14.5 (“The primary efficacy endpoint was the proportion of patients who improved by ≥2 steps on the DRSS from baseline to week 24 in the combined aflibercept groups and at week 52 in the 2Q16 and 2Q8 groups individually versus sham.”); MYL-AFL-BLA1079688 at -1079702–1079704, at Section 14.1; MYL-</p>

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	<p>AFL-BLA1079688 at -1079708–1079710, at Section 14.4; MYL-AFL0006405; MYL-AFL0004715; Brown 2021.</p> <p>In accordance with Mylan's proposed labeling, physicians will treat angiogenic eye disorders by administering aflibercept such that a patient will achieve the gain in visual acuity within 24 weeks after the initial dose.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at -1079704–1079706 at section 14.2 (“In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA compared to baseline. At week 24, the aflibercept 2 mg Q4 group was superior to the control group for the primary endpoint.”); MYL-AFL-BLA1079688 at -1079706–1079707, at section 14.3 (“In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline.”); MYL-AFL-BLA1079688 at -1079710–1079713, at section 14.5 (“The primary efficacy endpoint was the proportion of patients who improved by ≥2 steps on the DRSS from baseline to week 24 in the combined aflibercept groups and at week 52 in the 2Q16 and 2Q8 groups individually versus sham.”); MYL-AFL-BLA1079688 at -1079702–1079704, at Section 14.1; MYL-AFL0006405; MYL-AFL-BLA1079688 at -1079708–1079710, at Section 14.4; MYL-AFL0006405; MYL-AFL0004715; Brown 2021.</p>
10. The method of claim 2 wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.	<p>Administration of aflibercept in accordance with Mylan's proposed labeling practices claim 2 as set forth above.</p> <p>Mylan's proposed labeling directs physicians to administer aflibercept to treat angiogenic eye disorders such that a patient will gain at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with aflibercept) in the two studies (VIEW1 and VIEW2). In each study, up to week 52, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) aflibercept</p>

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	<p>administered 2 mg every 8 weeks following 3 initial monthly doses (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); 3) aflibercept 0.5 mg administered every 4 weeks (aflibercept 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4.”); MYL-AFL-BLA1079688 at -1079702–1079703, at section 14.1, tbl. 4 (showing that 31% (VIEW1 and VIEW2) of wet AMD patients treated with three monthly 2 mg doses of aflibercept followed by 2 mg doses administered once every 8 weeks gained at least 15 letters of vision (i.e., BCVA score)); MYL-AFL-BLA1079688 at -1079708–1079710, at Section 14.4; MYL-AFL-BLA1079688 at -1079710–1079713, at Section 14.5; MYL-AFL0006405; MYL-AFL0004715; Brown 2021.</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat angiogenic eye disorders by using the method of claim 2, resulting in a patient gaining at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with aflibercept) in the two studies (VIEW1 and VIEW2). In each study, up to week 52, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 3 initial monthly doses (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); 3) aflibercept 0.5 mg administered every 4 weeks (aflibercept 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4.”); MYL-AFL-BLA1079688 at -1079702–1079703, at section 14.1, tbl. 4 (showing that 31% (VIEW1 and VIEW2) of wet AMD patients treated with three monthly 2 mg doses of aflibercept followed by 2 mg doses administered once every 8 weeks gained at least 15 letters of vision (i.e., BCVA score)); MYL-AFL-BLA1079688 at -1079708–1079710, at Section 14.4; MYL-AFL0004715; MYL-AFL-BLA1079688 at -1079710–1079713, at Section 14.5; MYL-AFL0006405; MYL-AFL0004715; Brown 2021.</p>

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11. The method of claim 10 wherein only two secondary doses are administered to the patient.	<p>Administration of aflibercept in accordance with Mylan's proposed labeling practices claim 10 as set forth above.</p> <p>Mylan's proposed labeling directs physicians to treat angiogenic eye disorders by administering to the patient only two secondary doses.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information ("The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months . . ."); MYL-AFL-BLA1079688 at -107689, at section 2.2 ("The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months) . . .").</p> <p>In accordance with Mylan's proposed labeling, physicians will treat angiogenic eye disorders by administering to the patient only two secondary doses.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information ("The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months . . ."); MYL-AFL-BLA1079688 at -107689, at section 2.2 ("The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months) . . .").</p>
12. The method of claim 10 wherein the aflibercept is formulated as an isotonic solution.	<p>Administration of aflibercept in accordance with Mylan's proposed labeling practices claim 10 as set forth above.</p> <p>Mylan's M710 is a product biosimilar to and/or interchangeable with aflibercept that is formulated as an isotonic solution.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA0002879 at -0002881 (BLA section 3.2.P.2.2.1) ("M710 drug product (DP) has been developed as a biosimilar medicinal product of US-licensed reference product (RP) Eylea® (aflibercept), Regeneron Pharmaceuticals (RP), BLA 125387. Formulation development studies were directed</p>

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	<p>towards identification of a formulation that is comparable to RP.”); <i>id.</i> at -0002887 (BLA section 3.2.P.2.2.1.2.1.2) (“The osmolality of all six formulations is close to isotonic (Table 3.2.P.2.2-11.”); <i>id.</i> at -0002903 (tbl. 3.2.P.2.2-11).</p>
13. The method of claim 10 wherein the aflibercept is formulated with a nonionic surfactant.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 10 as set forth above.</p> <p>Mylan’s M710 is a product biosimilar to and/or interchangeable with aflibercept that is formulated with a nonionic surfactant.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA0002860 at -0002867 (“M710 is an aseptically filled drug product for intravitreal injection. It is a liquid being developed as a biosimilar to EYLEA® (aflibercept) injection; MYL-AFL-BLA0002860 at -0002868 (“Histidine buffer is a pH adjuster and Polysorbate 20 a nonionic surfactant.”); MYL-AFL-BLA0013850, at -13877; MYL-AFL-BLA10807972860 at -108833 (section 3.2.S.2.2.4.2.7) (██████████ Trehalose dihydrate, ██████████ PS20, pH 6.2 and ██████████ His-HCl, pH 6.2 is added to a final concentration of ██████████ Trehalose dihydrate, ██████████ PS20 and ██████████ protein concentration.”).</p>
14. The method of claim 1 wherein exclusion criteria for the patient include both of: (1) active ocular inflammation; and (2) active ocular or periocular infection.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 1 as set forth above.</p> <p>Mylan’s proposed labeling directs physicians to treat angiogenic eye disorders using the method of claim 1, excluding patients that have active intraocular inflammation or active ocular or periocular infection.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (listing as contraindications “Ocular or periocular infection” and “Active intraocular inflammation”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.1 (“YESAFILI is contraindicated in patients with ocular or periocular infections.”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.2 (“YESAFILI is contraindicated in patients with active intraocular inflammation.”).</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat angiogenic eye disorders by using the method of claim 1, excluding patients that have active intraocular inflammation or active ocular or periocular infection.</p>

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	<p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (listing as contraindications “Ocular or periocular infection” and “Active intraocular inflammation”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.1 (“YESAFILI is contraindicated in patients with ocular or periocular infections.”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.2 (“YESAFILI is contraindicated in patients with active intraocular inflammation.”).</p>
(15pre) 15. A method of treating diabetic macular edema in a patient in need thereof comprising	<p>Mylan’s proposed labeling directs physicians to treat diabetic macular edema (DME) by administering afibbercept.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILIT™ (afibbercept-jbv) is interchangeable* with EYLEA (afibbercept).”); MYL-AFL-BLA1079688, at -1079689 at section 1.3 (“YESAFILI is indicated for the treatment of . . . Diabetic Macular Edema (DME”).).</p> <p>In accordance with Mylan’s proposed labeling, physicians will administer afibbercept to treat diabetic macular edema.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILIT™ (afibbercept-jbv) is interchangeable* with EYLEA (afibbercept).”); MYL-AFL-BLA1079688 at -1079689, at section 1.3 (“YESAFILI is indicated for the treatment of . . . Diabetic Macular Edema (DME”).).</p>
(15a) sequentially administering to the patient a single initial dose of 2 mg of afibbercept, followed by one or more secondary doses of 2 mg of afibbercept, followed by one or more tertiary doses of 2 mg of afibbercept;	<p>Mylan’s proposed labeling directs physicians to treat diabetic macular edema by administering a single initial dose of 2 mg of afibbercept, followed by one or more secondary doses of 2 mg of afibbercept, followed by one or more tertiary doses of 2 mg of afibbercept.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at -1079689, at section 2.4 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”).</p>

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	<p>In accordance with Mylan's proposed labeling, physicians will treat diabetic macular edema by administering a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079689, at section 2.4 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”).</i></p>
(15b) wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and	<p>Mylan's proposed labeling directs physicians to treat diabetic macular edema by administering each secondary dose to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079689, at section 2.4 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”).</i></p> <p>In accordance with Mylan's proposed labeling, physicians will treat diabetic macular edema by administering each secondary dose to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079689, at section 2.4 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”).</i></p>
(15c) wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose.	<p>Mylan's proposed labeling directs physicians to treat diabetic macular edema by administering each tertiary dose to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079689, at section 2.4 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or</i></p>

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	<p>50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”).</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat diabetic macular edema by administering each tertiary dose to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079689, at section 2.4 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”).</i></p>
16. The method of claim 15 wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 15 as set forth above.</p> <p>Mylan’s proposed labeling directs physicians to administer aflibercept to treat diabetic macular edema such that a patient will achieve a gain in visual acuity within 52 weeks after the initial dose.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Both aflibercept 2Q8 and aflibercept 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group in year 1.”); MYL-AFL-BLA1079688 at -1079704–1079706, at section 14.2 (“In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA compared to baseline. At week 24, the aflibercept 2 mg Q4 group was superior to the control group for the primary endpoint.”); MYL-AFL-BLA1079688 at -1079706–1079707, at section 14.3 (“In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline.”); MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4 (“In both studies, the primary efficacy endpoint was the mean</i></p>

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	<p>change from baseline in BCVA at week 52 as measured by ETDRS letter score.”); MYL-AFL-BLA1079688 at -1079710–1079713, at section 14.5 (“The primary efficacy endpoint was the proportion of patients who improved by ≥ 2 steps on the DRSS from baseline to week 24 in the combined aflibercept groups and at week 52 in the 2Q16 and 2Q8 groups individually versus sham.”); MYL-AFL0004715; MYL-AFL-BLA1079688 at -1079708–1079710, at Section 14.4 (Table 7 & Fig. 16)).</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat diabetic macular edema by administering aflibercept such that a patient will achieve a gain in visual acuity within 52 weeks after the initial dose.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Both aflibercept 2Q8 and aflibercept 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group in year 1.”); MYL-AFL-BLA1079688 at -1079704–1079706, at section 14.2 (“In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA compared to baseline. At week 24, the aflibercept 2 mg Q4 group was superior to the control group for the primary endpoint.”); MYL-AFL-BLA1079688 at -1079706–1079707, at section 14.3 (“In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline.”); MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4 (“In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score.”); MYL-AFL-BLA1079688 at -1079710–1079713, at section 14.5 (“The primary efficacy endpoint was the proportion of patients who improved by ≥ 2 steps on the DRSS from baseline to week 24 in the combined aflibercept groups and at week 52 in the 2Q16 and 2Q8 groups individually versus sham.”); MYL-AFL-BLA1079688 at -1079708–1079710, at Section 14.4 (“In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score. Efficacy of both aflibercept 2Q8 and aflibercept 2Q4 groups was statistically superior to the control group. This statistically superior</p>

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	improvement in BCV A was maintained at week 100 in both studies.”); <i>id.</i> (Table 7 & Fig. 16); MYL-AFL0004715.
17. The method of claim 16 wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 16 as set forth above.</p> <p>Mylan’s proposed labeling directs physicians to administer aflibercept to treat diabetic macular edema such that a patient will gain at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFIL™ (aflibercept-jbv) is interchangeable* with EYLEA (aflibercept.”); MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 23 to 87 years with a mean of 63 years. Of those, 576 were randomized to aflibercept groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 5 initial monthly injections (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the aflibercept groups could receive laser and patients in the laser group could receive aflibercept. In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score.”); MYL-AFL-BLA1079688 at -1079708–1079709, at section 14.4, tbl. 7 (showing that 33.3% of 2Q8 DME patients (VIVID) and 33.1% of 2Q8 DME patients (VISTA) gained at least 15 letters in BCVA from baseline); MYL-AFL0004715.</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat diabetic macular edema by using the method of claim 16, resulting in a patient gaining at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early</p>

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	<p>Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g.,</i> MYL-AFL- at Highlights of Prescribing Information (“YESAFILI™ (aflibercept-jbvf) is interchangeable* with EYLEA (aflibercept.”); MYL-AFL-BLA1079688 at - 1079708–1079710, at section 14.4 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 23 to 87 years with a mean of 63 years. Of those, 576 were randomized to aflibercept groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 5 initial monthly injections (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the aflibercept groups could receive laser and patients in the laser group could receive aflibercept. In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score.”); MYL-AFL-BLA1079688 at -1079708–1079709, at section 14.4, tbl. 7 (showing that 33.3% of 2Q8 DME patients (VIVID) and 33.1% of 2Q8 DME patients (VISTA) gained at least 15 letters in BCVA from baseline); MYL-AFL0004715.</p>
18. The method of claim 17 wherein the aflibercept is formulated as an isotonic solution.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 17 as set forth above.</p> <p>Mylan’s M710 is a product biosimilar to and/or interchangeable with aflibercept that is formulated as an isotonic solution.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA0002879 at -0002881 (BLA section 3.2.P.2.2.1) (“M710 drug product (DP) has been developed as a biosimilar medicinal product of US-licensed reference product (RP) Eylea® (aflibercept), Regeneron Pharmaceuticals (RP), BLA 125387. Formulation development studies were directed towards identification of a formulation that is comparable to</p>

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19. The method of claim 17 wherein the aflibercept is formulated with a non-ionic surfactant.	<p>Administration of aflibercept in accordance with Mylan's proposed labeling practices claim 17 as set forth above.</p> <p>Mylan's M710 is a product biosimilar to and/or interchangeable with aflibercept that is formulated with a nonionic surfactant.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA0002860 at -0002867 ("M710 is an aseptically filled drug product for intravitreal injection. It is a liquid being developed as a biosimilar to EYLEA® (aflibercept) injection; MYL-AFL-BLA0002860 at -0002868 ("Histidine buffer is a pH adjuster and Polysorbate 20 a nonionic surfactant."); MYL-AFL-BLA0013850, at -13877; MYL-AFL-BLA108079 at -1080833 (section 3.2.S.2.2.4.2.7) [REDACTED] Trehalose dihydrate, [REDACTED] PS20, pH 6.2 and [REDACTED] His-HCl, pH 6.2 is added to a final concentration of Trehalose dihydrate, [REDACTED] PS20 and [REDACTED] protein concentration.").</p>
20. The method of claim 17 wherein the patient achieves a gain in visual acuity within 24 weeks following the initial dose.	<p>Administration of aflibercept in accordance with Mylan's proposed labeling practices claim 17 as set forth above.</p> <p>Mylan's proposed labeling directs physicians to administer aflibercept to treat diabetic macular edema such that a patient will achieve the gain in visual acuity within 24 weeks after the initial dose.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4, tbl. 7, fig. 16 (showing a gain in visual acuity within 24 weeks); MYL-AFL-BLA1079688 at -1079710–1079713, at section 14.5 ("In the VIVID and VISTA studies, an efficacy outcome was the change in the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (ETDRS-DRSS). The ETDRS-DRSS score was assessed at baseline and approximately every 6 months thereafter for the duration of the studies [<i>see Clinical Studies (14.4)</i>."]); MYL-AFL-BLA1079688 at -1079710–1079713, at section 14.5 ("The primary efficacy endpoint was the proportion of patients who improved by ≥2 steps on the DRSS from baseline to week 24 in the combined aflibercept groups</p>

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	<p>and at week 52 in the 2Q16 and 2Q8 groups individually versus sham.”); MYL-AFL0004715.</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat angiogenic eye disorders by administering aflibercept such that a patient will achieve the gain in visual acuity within 24 weeks after the initial dose.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at -1079708–1079710 at section 14.4, tbl. 7, fig. 16 (showing a gain in visual acuity within 24 weeks); MYL-AFL-BLA1079688 at -1079710–1079713, at section 14.5 (“In the VIVID and VISTA studies, an efficacy outcome was the change in the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (ETDRS-DRSS). The ETDRS-DRSS score was assessed at baseline and approximately every 6 months thereafter for the duration of the studies [<i>see Clinical Studies (14.4)</i>.”]; MYL-AFL-BLA1079688 at -1079710–1079713, at section 14.5 (“The primary efficacy endpoint was the proportion of patients who improved by ≥ 2 steps on the DRSS from baseline to week 24 in the combined aflibercept groups and at week 52 in the 2Q16 and 2Q8 groups individually versus sham.”); MYL-AFL0004715.</p>
21. The method of claim 16 wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 16 as set forth above.</p> <p>Mylan’s proposed labeling directs physicians to administer aflibercept to treat diabetic macular edema such that a patient will gain at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILIT™ (aflibercept-jbv) is interchangeable* with EYLEA (aflibercept).”); MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 23 to 87 years with a mean of 63 years. Of those, 576 were randomized to aflibercept groups in the two studies (VIVID and VISTA). In</p>

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	<p>each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 5 initial monthly injections (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the aflibercept groups could receive laser and patients in the laser group could receive aflibercept. In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score.”); MYL-AFL-BLA1079688 at -1079708–1079709, at section 14.4, tbl. 7 (showing that 33.3% of 2Q8 DME patients (VIVID) and 33.1% of 2Q8 DME patients (VISTA) gained at least 15 letters in BCVA from baseline); MYL-AFL-BLA1079688 at -1079709–1079710, at section 14.4, fig. 16; MYL-AFL0004715.</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat diabetic macular edema by using the method of claim 16, resulting in a patient gaining at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFIL™ (aflibercept-jbvf) is interchangeable* with EYLEA (aflibercept.”); MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 23 to 87 years with a mean of 63 years. Of those, 576 were randomized to aflibercept groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 5 initial monthly injections (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the aflibercept groups could</p>

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	receive laser and patients in the laser group could receive aflibercept. In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score."); MYL-AFL-BLA1079688 at -1079708–1079709, at section 14.4, tbl. 7 (showing that 33.3% of 2Q8 DME patients (VIVID) and 33.1% of 2Q8 DME patients (VISTA) gained at least 15 letters in BCVA from baseline); MYL-AFL-BLA1079688 at -1079709–1079710, at section 14.4 (fig. 16); MYL-AFL0004715.
22. The method of claim 21 wherein the aflibercept is formulated as an isotonic solution.	<p>Administration of aflibercept in accordance with Mylan's proposed labeling practices claim 21 as set forth above.</p> <p>Mylan's M710 is a product biosimilar to and/or interchangeable with aflibercept that is formulated as an isotonic solution.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA0002879 at -0002881 (BLA section 3.2.P.2.2.1) ("M710 drug product (DP) has been developed as a biosimilar medicinal product of US-licensed reference product (RP) Eylea® (aflibercept), Regeneron Pharmaceuticals (RP), BLA 125387. Formulation development studies were directed towards identification of a formulation that is comparable to RP."); <i>id.</i> at -0002887 (BLA section 3.2.P.2.2.1.2.1.2) ("The osmolality of all six formulations is close to isotonic (Table 3.2.P.2.2-11."); <i>id.</i> at -0002903 (tbl. 3.2.P.2.2-11).</p>
23. The method of claim 21 wherein the aflibercept is formulated with a nonionic surfactant.	<p>Administration of aflibercept in accordance with Mylan's proposed labeling practices claim 21 as set forth above.</p> <p>Mylan's M710 is a product biosimilar to and/or interchangeable with aflibercept that is formulated with a nonionic surfactant.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA0002860 at -0002867 ("M710 is an aseptically filled drug product for intravitreal injection. It is a liquid being developed as a biosimilar to EYLEA® (aflibercept) injection; MYL-AFL-BLA0002860 at -0002868 ("Histidine buffer is a pH adjuster and Polysorbate 20 a nonionic surfactant."); MYL-AFL-BLA0013850, at -13877; MYL-AFL-BLA108079 at -1080833 (section 3.2.S.2.2.4.2.7) [REDACTED] Trehalose dihydrate, [REDACTED] PS20, pH 6.2 and His-HCl, pH 6.2 is added to a final concentration of [REDACTED]</p>

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	Trehalose dihydrate, [REDACTED] PS20 and [REDACTED] protein concentration.”).
25. The method of claim 15 wherein four secondary doses are administered to the patient.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 15 as set forth above.</p> <p>Mylan’s proposed labeling directs physicians to treat DME by administering four secondary doses of aflibercept.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing that, for the treatment of DME and DR, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months”); MYL-AFL-BLA1079688 at - 1079689, at section 2.4 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”)).</i></p> <p>In accordance with Mylan’s proposed labeling, physicians will treat DME by administering four secondary doses of aflibercept.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing that, for the treatment of DME and DR, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months”); MYL-AFL-BLA1079688 at - 1079689, at section 2.4 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”)).</i></p>
(26pre) 26. A method of treating age related macular degeneration in a patient in need thereof comprising	<p>Mylan’s proposed labeling directs physicians to treat age related macular degeneration (AMD) by administering aflibercept.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILITM (aflibercept-jbv) is</i></p>

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	<p>interchangeable* with EYLEA (aflibercept)."); MYL-AFL-BLA1079688 at -1079689, at section 1.1 ("YESAFILI is indicated for the treatment of . . . Neovascular (Wet) Age-Related Macular Degeneration (AMD").).</p> <p>In accordance with Mylan's proposed labeling, physicians will administer aflibercept to treat AMD.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information ("YESAFILIT™ (aflibercept-jbvf) is interchangeable* with EYLEA (aflibercept)."); MYL-AFL-BLA1079688 at -1079689, at section 1.1 ("YESAFILI is indicated for the treatment of . . . Neovascular (Wet) Age-Related Macular Degeneration (AMD").).</p>
(26a) sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;	<p>Mylan's proposed labeling directs physicians to treat wet AMD by administering a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing that, for the treatment of wet AMD, "[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)").</p> <p>In accordance with Mylan's proposed labeling, physicians will treat wet AMD by administering a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing that, for the treatment of wet AMD, "[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)").</p>

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(26b) wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and	<p>Mylan's proposed labeling directs physicians to treat wet AMD by administering each secondary dose of 2 mg of afibercept by intravitreal injection approximately 4 weeks after the immediately preceding dose.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months . . .”); MYL-AFL-BLA1079688 at -1079689, at section 2.2 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months) . . .”).</p> <p>In accordance with Mylan's proposed labeling, physicians will treat wet AMD by administering each secondary dose of 2 mg of afibercept by intravitreal injection approximately 4 weeks after the immediately preceding dose.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months . . .”); MYL-AFL-BLA1079688 at -1079689, at section 2.2 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months) . . .”).</p>
(26c) wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose;	<p>Mylan's proposed labeling directs physicians to treat wet AMD by administering each tertiary dose of 2 mg of afibercept by intravitreal injection approximately 8 weeks after the immediately preceding dose.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”); MYL-AFL-BLA1079688 at -1079689, at section 2.2 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28</p>

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	<p>days, monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”).</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat wet AMD by administering each tertiary dose of 2 mg of aflibercept by intravitreal injection approximately 8 weeks after the immediately preceding dose.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”); MYL-AFL-BLA1079688 at -1079689, at section 2.2 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”).</p>
(26d) wherein the method is as effective in achieving a gain in visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose.	<p>Mylan’s proposed labeling directs physicians to administer aflibercept to treat AMD according to a method that is as effective in achieving a gain in visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Both aflibercept 2Q8 and aflibercept 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group in year 1.”); MYL-AFL-BLA1079688 at -1079702–1079703, at section 14.1, tbl. 4; MYL-AFL0006405.</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat AMD according to a method that is as effective in achieving a gain in visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human</p>

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	<p>subjects with age-related macular degeneration at 52 weeks following the initial dose.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Both aflibercept 2Q8 and aflibercept 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group in year 1.”); MYL-AFL-BLA1079688 at -1079702–1079703, at section 14.1, tbl. 4; MYL-AFL0006405.</p>
27. The method of claim 26 wherein only two secondary doses are administered to the patient.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 26 as set forth above.</p> <p>Mylan’s proposed labeling directs physicians to treat AMD by administering to the patient only two secondary doses.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months . . .”); MYL-AFL-BLA1079688 at -1079689, at section 2.2 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months) . . .”); MYL-AFL-BLA1079688 at -1079702–1079704, at Section 14.1.</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat AMD by administering to the patient only two secondary doses.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months . . .”); MYL-AFL-BLA1079688 at -1079689, at section 2.2 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months) . . .”); MYL-AFL-BLA1079688 at -1079702–1079704, at Section 14.1.</p>

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28. The method of claim 26 wherein the gain in visual acuity is measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.	<p>Administration of aflibercept in accordance with Mylan's proposed labeling practices claim 26 as set forth above.</p> <p>Mylan's proposed labeling directs physicians to administer aflibercept to treat wet AMD according to a method where the gain in visual acuity is measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with aflibercept) in the two studies (VIEW1 and VIEW2). In each study, up to week 52, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 3 initial monthly doses (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); 3) aflibercept 0.5 mg administered every 4 weeks (aflibercept 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4.”); MYL-AFL-BLA1079688 at -1079702–1079703, at section 14.1, tbl. 4 (showing that 31% (VIEW1 and VIEW2) of wet AMD patients treated with three monthly 2 mg doses of aflibercept followed by 2 mg doses administered once every 8 weeks gained at least 15 letters of vision (i.e., BCVA score)); MYL-AFL0006405.</i></p> <p>In accordance with Mylan's proposed labeling, physicians will treat wet AMD according to a method where the gain in visual acuity is measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with aflibercept) in the two studies (VIEW1 and VIEW2). In each study, up to week 52, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 3 initial monthly</i></p>

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	doses (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); 3) aflibercept 0.5 mg administered every 4 weeks (aflibercept 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4.”); MYL-AFL-BLA1079688 at -1079702–1079703, at section 14.1, tbl. 4 (showing that 31% (VIEW1 and VIEW2) of wet AMD patients treated with three monthly 2 mg doses of aflibercept followed by 2 mg doses administered once every 8 weeks gained at least 15 letters of vision (i.e., BCVA score)); MYL-AFL0006405.
(29pre) 29. A method of treating age-related macular degeneration in a patient in need thereof comprising	<p>Mylan's proposed labeling directs physicians to treat age related macular degeneration (AMD) by administering aflibercept.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILIT™ (aflibercept-jbvf) is interchangeable* with EYLEA (aflibercept).”); MYL-AFL-BLA1079688, at -1079689 at section 1.1 (“YESAFILI is indicated for the treatment of . . . Neovascular (Wet) Age-Related Macular Degeneration (AMD”).).</p> <p>In accordance with Mylan's proposed labeling, physicians will administer aflibercept to treat AMD.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILIT™ (aflibercept-jbvf) is interchangeable* with EYLEA (aflibercept).”); MYL-AFL-BLA1079688, at -1079689, at section 1.1 (“YESAFILI is indicated for the treatment of . . . Neovascular (Wet) Age-Related Macular Degeneration (AMD”).).</p>
(29a) sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;	<p>Mylan's proposed labeling directs physicians to treat wet AMD by administering a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing that, for the treatment of wet AMD, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once</p>

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	<p>every 8 weeks (2 months”); MYL-AFL-BLA1079688 at - 1079689, at section 2.2 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months) . . .”).</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat wet AMD by administering a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing that, for the treatment of wet AMD, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months”); MYL-AFL-BLA1079688 at - 1079689, at section 2.2 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months) . . .”).</p>
(29b) wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and	<p>Mylan’s proposed labeling directs physicians to treat wet AMD by administering each secondary dose of 2 mg of aflibercept by intravitreal injection approximately 4 weeks after the immediately preceding dose.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months . . .”); MYL-AFL-BLA1079688 at -1079689, at section 2.2 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months) . . .”).</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat wet AMD by administering each secondary dose of 2 mg of aflibercept by intravitreal injection approximately 4 weeks after the immediately preceding dose.</p>

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	<p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months . . .”); MYL-AFL-BLA1079688 at -1079689, at section 2.2 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months) . . .”).</p>
(29c) wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose;	<p>Mylan’s proposed labeling directs physicians to treat wet AMD by administering each tertiary dose of 2 mg of aflibercept by intravitreal injection approximately 8 weeks after the immediately preceding dose.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”); MYL-AFL-BLA1079688 at -1079689 at section 2.2 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”).</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat wet AMD by administering each tertiary dose of 2 mg of aflibercept by intravitreal injection approximately 8 weeks after the immediately preceding dose.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”); MYL-AFL-BLA1079688 at -1079689, at section 2.2 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months), followed by 2</p>

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	mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”).
(29d) wherein the method is as effective in maintaining visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose.	<p>Mylan’s proposed labeling directs physicians to administer aflibercept to treat AMD according to a method that is as effective in maintaining visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Both aflibercept 2Q8 and aflibercept 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group in year 1.”); MYL-AFL0006405.</i></p> <p>In accordance with Mylan’s proposed labeling, physicians will treat AMD according to a method that is as effective in maintaining visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Both aflibercept 2Q8 and aflibercept 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group in year 1.”); MYL-AFL0006405.</i></p>
30. The method of claim 29 wherein maintenance of visual acuity means loss of less than 15 letters Best Corrected Visual Acuity (BCVA) as measured by using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 29 as set forth above.</p> <p>Mylan’s proposed labeling directs physicians to administer aflibercept to treat wet AMD according to a method where maintenance of visual acuity means loss of less than 15 letters Best Corrected Visual Acuity (BCVA) as measured by using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p>

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	<p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILIT™ (aflibercept-jbvf) is interchangeable* with EYLEA (aflibercept).”); MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with aflibercept) in the two studies (VIEW1 and VIEW2). In each study, up to week 52, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 3 initial monthly doses (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); 3) aflibercept 0.5 mg administered every 4 weeks (aflibercept 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4). In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline.”); MYL-AFL-BLA1079688 at -1079702–1079703, at section 14.1, tbl. 4 (showing that 94% (VIEW1) and 95% (VIEW2) of wet AMD patients treated with three monthly 2 mg doses of aflibercept followed by 2 mg doses administered once every 8 weeks maintained visual acuity (%) (<15 letters of BCVA loss)); MYL-AFL0006405.</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat wet AMD according to a method where maintenance of visual acuity means loss of less than 15 letters Best Corrected Visual Acuity (BCVA) as measured by using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILIT™ (aflibercept-jbvf) is interchangeable* with EYLEA (aflibercept).”); MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with aflibercept) in the two studies (VIEW1 and VIEW2). In each study, up to week 52, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 3 initial monthly doses (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); 3) aflibercept 0.5 mg administered every 4 weeks (aflibercept 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4). In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline.”); MYL-AFL-BLA1079688 at -1079702–1079703, at section 14.1, tbl. 4 (showing that 94% (VIEW1) and 95% (VIEW2) of wet AMD patients treated with three monthly 2 mg doses of aflibercept followed by 2 mg doses administered once every 8 weeks maintained visual acuity (%) (<15 letters of BCVA loss)); MYL-AFL0006405.</p>

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	<p>weeks following 3 initial monthly doses (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); 3) aflibercept 0.5 mg administered every 4 weeks (aflibercept 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4). In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline.”); MYL-AFL-BLA1079688 at - 1079702–1079703, at section 14.1, tbl. 4 (showing that 94% (VIEW1) and 95% (VIEW2) of wet AMD patients treated with three monthly 2 mg doses of aflibercept followed by 2 mg doses administered once every 8 weeks maintained visual acuity (%) (<15 letters of BCVA loss)); MYL-AFL0006405.</p>

APPENDIX D

APPENDIX D

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(1pre) 1. A method for treating age related macular degeneration in a patient in need thereof,	<p>Mylan's proposed labeling directs physicians to treat age related macular degeneration (AMD) by administering afibbercept.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information ("YESAFILITM (afibbercept-jbv) is interchangeable* to EYLEA (afibbercept)."); MYL-AFL-BLA1079688 at -1079689, at section 1.1 ("YESAFILI is indicated for the treatment of . . . Neovascular (Wet) Age-Related Macular Degeneration (AMD).").</p> <p>In accordance with Mylan's proposed labeling, physicians will administer afibbercept to treat age related macular degeneration.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing administration of afibbercept to treat, <i>inter alia</i>, neovascular (wet) age-related macular degeneration (AMD)); MYL-AFL-BLA1079688 at -1079689, at section 1.1 ("YESAFILI is indicated for the treatment of . . . Neovascular (Wet) Age-Related Macular Degeneration (AMD).").</p>
(1a) comprising intravitreally administering, to said patient, an effective amount of afibbercept which is 2 mg approximately every 4 weeks for the first 3 months,	<p>Mylan's proposed labeling directs physicians to treat wet AMD by administering 2 mg of afibbercept every 4 weeks for the first 3 months.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information ("The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months"); MYL-AFL-BLA1079688 at -1079689, at section 2.2 ("The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months)")</p> <p>In accordance with Mylan's proposed labeling, physicians will treat wet AMD by administering 2 mg of afibbercept every 4 weeks for the first 3 months.</p>

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	<p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months . . .”); MYL-AFL-BLA1079688 at -1079689 section 2.2 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months) . . .”).</p>
(1b) followed by 2 mg approximately once every 8 weeks or once every 2 months.	<p>Following administration of 2 mg of aflibercept every 4 weeks for the first 3 months, as directed by Mylan’s proposed labeling for the treatment of wet AMD, Mylan’s proposed labeling directs physicians to administer 2 mg (0.05 mL) via intravitreal injection once every 8 weeks or once every 2 months to treat wet AMD.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”); MYL-AFL-BLA1079688 at -1079689, at section 2.2 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”).</p> <p>In accordance with Mylan’s proposed labeling, following administration of 2 mg of aflibercept every 4 weeks for the first 3 months, physicians will administer 2 mg (0.05 mL) via intravitreal injection once every 8 weeks or once every 2 months to treat wet AMD.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”); MYL-AFL-BLA1079688 at -1079689, at section 2.2 (“The</p>

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	recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”).
2. The method of claim 1, wherein the age-related macular degeneration is neovascular (wet).	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 1 as set forth above.</p> <p>Mylan’s proposed labeling directs physicians to treat neovascular (wet) age-related macular degeneration (AMD) using the method of claim 1.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILITM (aflibercept-jbvf) is interchangeable* to EYLEA (aflibercept.”); MYL-AFL-BLA1079688 at section 1.1 (“YESAFILI is indicated for the treatment of . . . Neovascular (Wet) Age-Related Macular Degeneration (AMD”)).</i></p> <p>In accordance with Mylan’s proposed labeling, physicians will treat wet AMD by using the method of claim 1.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILITM (aflibercept-jbvf) is interchangeable* to EYLEA (aflibercept.”); MYL-AFL-BLA1079688 at -1079689, at section 1.1 (“YESAFILI is indicated for the treatment of . . . Neovascular (Wet) Age-Related Macular Degeneration (AMD”)).</i></p>
5. The method of claim 2 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 2 as set forth above.</p> <p>Mylan’s proposed labeling indicates that M710 (YESAFILI) is interchangeable with EYLEA (aflibercept), which, according to Mylan’s proposed labeling, means it is “a biological product that is approved based on data demonstrating that it is highly similar to an FDA-approved reference product (RP) and that there are no clinically meaningful differences between the products; it can be expected to produce the same clinical result as the RP in any given patient; and if administered more than once to a patient, the risk in terms of safety or diminished efficacy from alternating or switching between the use of the RP</p>

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	<p>and IP is not greater than that from the PR without such alternation or switch . Interchangeability of YESAFILI has been demonstrated for the condition(s) of use, strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.” Mylan’s proposed labeling includes the results for clinical studies that assessed the safety and efficacy of aflibercept. Because M710 must be highly similar to EYLEA (aflibercept) and must not have any clinically meaningful differences compared to EYLEA (aflibercept) (the reference product), and because the clinical study results for treating wet AMD by administering aflibercept, which are included in Mylan’s proposed labeling, show that patients gained at least 15 letters of Best Corrected Visual Acuity (BCVA) score, Mylan’s proposed labeling directs physicians to administer YESAFILI (M710) to treat wet AMD such that a patient will gain at least 15 letters of Best Corrected Visual Acuity (BCVA) score.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILITM (aflibercept-jbv) is interchangeable* to EYLEA (aflibercept.”); MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with aflibercept) in the two studies (VIEW1 and VIEW2). In each study, up to week 52, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 3 initial monthly doses (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); 3) aflibercept 0.5 mg administered every 4 weeks (aflibercept 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4.”); MYL-AFL-BLA1079688 at -1079702–1079703, at section 14.1, tbl. 4 (showing that 31% (VIEW1 and VIEW2) of wet AMD patients treated with three monthly 2 mg doses of aflibercept followed by 2 mg doses administered once every 8 weeks gained at least 15 letters of vision (i.e., BCVA score)); MYL-AFL0006405.</i></p> <p>In accordance with Mylan’s proposed labeling, physicians will treat wet AMD by using the method of claim 2,</p>

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	<p>resulting in a patient gaining at least 15 letters of Best Corrected Visual Acuity (BCVA) score.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079702–1079704, at section 14.1 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with aflibercept) in the two studies (VIEW1 and VIEW2). In each study, up to week 52, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 3 initial monthly doses (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); 3) aflibercept 0.5 mg administered every 4 weeks (aflibercept 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4.”); MYL-AFL-BLA1079688 at -1079702–1079703, at section 14.1, tbl. 4 (showing that 31% (VIEW1 and VIEW2) of wet AMD patients treated with three monthly 2 mg doses of aflibercept followed by 2 mg doses administered once every 8 weeks gained at least 15 letters of vision (i.e., BCVA score)); MYL-AFL0006405.</i></p>
6. The method of claim 5 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 5 as set forth above.</p> <p>In the wet AMD clinical study results shown in Mylan’s proposed labeling, which direct physicians to treat wet AMD using the method of claim 5, the mean change in BCVA was measured by ETDRS letter score from baseline, so the BCVA score corresponded to the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at 1079702–1079703, at section 14.1, tbl. 4; MYL-AFL0006405.</i></p>
7. The method of claim 1, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 1 as set forth above.</p> <p>Mylan’s proposed labeling instruct physicians that every 4 weeks comprises approximately every 28 days or approximately monthly.</p>

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	<p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months . . .”); MYL-AFL-BLA1079688 at -1079689, at section 2.2 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months) . . .”).</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat wet AMD by administering 2 mg of aflibercept every 4 weeks for the first 3 months, where every 4 weeks is approximately every 28 days or approximately monthly.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“The recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months . . .”); MYL-AFL-BLA1079688 at -1079689, at section 2.2 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months) . . .”).</p>
8. The method of claim 7, wherein the age-related macular degeneration is neovascular (wet).	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 7 as set forth above.</p> <p>Mylan’s proposed labeling directs physicians to treat neovascular (wet) age-related macular degeneration (AMD) using the method of claim 7.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILITM (aflibercept-jbvf) is interchangeable* to EYLEA (aflibercept).”); MYL-AFL-BLA1079688 at -1079689, at section 1.1 (“YESAFILI is indicated for the treatment of . . . Neovascular (Wet) Age-Related Macular Degeneration (AMD)”).</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat wet AMD by using the method of claim 7.</p>

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	<p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILIT™ (afibbercept-jbvf) is interchangeable* to EYLEA (afibbercept.”); MYL-AFL-BLA1079688 at -1079689, at section 1.1 (“YESAFILI is indicated for the treatment of . . . Neovascular (Wet) Age-Related Macular Degeneration (AMD”)).</p>
9. The method of claim 8 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.	<p>Administration of afibbercept in accordance with Mylan’s proposed labeling practices claim 8 as set forth above.</p> <p>Mylan’s proposed labeling directs physicians to treat neovascular (wet) age-related macular degeneration (AMD) using the method of claim 8, excluding patients that have active intraocular inflammation or active ocular or periocular infection.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (listing as contraindications “Ocular or periocular infection” and “Active intraocular inflammation”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.1 (“YESAFILI is contraindicated in patients with ocular or periocular infections.”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.2 (“YESAFILI is contraindicated in patients with active intraocular inflammation.”).</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat wet AMD by using the method of claim 8, excluding patients that have active intraocular inflammation or active ocular or periocular infection.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (listing as contraindications “Ocular or periocular infection” and “Active intraocular inflammation”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.1 (“YESAFILI is contraindicated in patients with ocular or periocular infections.”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.2 (“YESAFILI is contraindicated in patients with active intraocular inflammation.”).</p>
(10pre) 10. A method for treating diabetic macular	<p>Mylan’s proposed labeling directs physicians to treat diabetic macular edema (DME) by administering afibbercept.</p>

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edema in a patient in need thereof,	<p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILIT™ (afibbercept-jbvf) is interchangeable* to EYLEA (afibbercept.”); MYL-AFL-BLA1079688 at -107969, at section 1.3 (“YESAFILI is indicated for the treatment of . . . Diabetic Macular Edema (DME”.”).</p> <p>In accordance with Mylan’s proposed labeling, physicians will administer afibbercept to treat DME.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILIT™ (afibbercept-jbvf) is interchangeable* to EYLEA (afibbercept.”); MYL-AFL-BLA1079688 at -107969, at section 1.3 (“YESAFILI is indicated for the treatment of . . . Diabetic Macular Edema (DME”.”).</p>
(10a) comprising intravitreally administering, to said patient, an effective amount of afibbercept which is 2 mg approximately every 4 weeks for the first 5 injections,	<p>Mylan’s proposed labeling directs physicians to treat DME by administering 2 mg of afibbercept approximately every 4 weeks for the first 5 injections.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at -1079689, at section 2.4 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections . . .”).</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat DME by administering 2 mg of afibbercept approximately every 4 weeks for the first 5 injections.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688, at -1079689, at section 2.4 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections . . .”).</p>
(10b) followed by 2 mg approximately once every 8 weeks or once every 2 months.	<p>Following administration of 2 mg of afibbercept approximately every 4 weeks for the first 5 injections, as directed by Mylan’s proposed labeling for the treatment of DME, Mylan’s proposed labeling directs physicians to administer 2 mg (0.05 mL) of afibbercept via intravitreal</p>

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	<p>injection once every 8 weeks or once every 2 months to treat diabetic macular edema.</p> <p><i>See, e.g., MYL-AFL-BLA1079688, at -1079689, at section 2.4 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”).</i></p> <p>In accordance with Mylan’s proposed labeling, following administration of 2 mg of aflibercept every 4 weeks for the first 5 injections, physicians will administer 2 mg (0.05 mL) via intravitreal injection once every 8 weeks or once every 2 months to treat DME.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079689, at section 2.4 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”).</i></p>
11. The method of claim 10, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 10 as set forth above.</p> <p>Mylan’s proposed labeling instruct physicians that every 4 weeks comprises approximately every 28 days or approximately monthly.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079689 at section 2.4 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections . . . ”).</i></p> <p>In accordance with Mylan’s proposed labeling, physicians will treat DME by administering 2 mg of aflibercept every 4 weeks for the first 3 months, where every 4 weeks is approximately every 28 days or approximately monthly.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079689, at section 2.4 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4</i></p>

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	weeks (approximately every 28 days, monthly) for the first 5 injections . . . ”).
12. The method of claim 10, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 10 as set forth above.</p> <p>Following administration of 2 mg of aflibercept approximately every 4 weeks for the first 5 injections, as directed by Mylan’s proposed labeling for the treatment of diabetic macular edema, after 20 weeks, Mylan’s proposed labeling directs physicians to administer 2 mg (0.05 mL) of aflibercept once every 4 weeks to treat diabetic macular edema.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079689, at section 2.4 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months.”).</i></p> <p>In accordance with Mylan’s proposed labeling, following administration of 2 mg of aflibercept every 4 weeks for the first 5 injections, after 20 weeks, physicians will administer 2 mg (0.05 mL) via intravitreal injection once every 4 weeks to treat diabetic macular edema.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079689, at section 2.4 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months.”).</i></p>
15. The method of claim 10 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 10 as set forth above.</p> <p>Mylan’s proposed labeling indicates that M710 (YESAFILI) is interchangeable with EYLEA (aflibercept), which, according to Mylan’s proposed labeling, means it is</p>

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	<p>“a biological product that is approved based on data demonstrating that it is highly similar to an FDA-approved reference product (RP) and that there are no clinically meaningful differences between the products; it can be expected to produce the same clinical result as the RP in any given patient; and if administered more than once to a patient, the risk in terms of safety or diminished efficacy from alternating or switching between the use of the RP and IP is not greater than that from the PR without such alternation or switch . Interchangeability of YESAFILI has been demonstrated for the condition(s) of use, strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.” Mylan’s proposed labeling includes the results for clinical studies that assessed the safety and efficacy of aflibercept in studies in patients with DME. Because M710 must be highly similar to EYLEA (aflibercept) and must not have any clinically meaningful differences compared to EYLEA (aflibercept) (the reference product), and because the clinical study results for treating DME by administering aflibercept using the method of claim 10, which are included in Mylan’s proposed labeling, show that patients gained at least 15 letters of Best Corrected Visual Acuity (BCVA) score, Mylan’s proposed labeling directs physicians to administer YESAFILI (M710) to treat DME such that a patient will gain at least 15 letters of Best Corrected Visual Acuity (BCVA) score.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILI™ (aflibercept-jbv) is interchangeable* to EYLEA (aflibercept).”); MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 23 to 87 years with a mean of 63 years. Of those, 576 were randomized to aflibercept groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 5 initial monthly injections (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); and 3) macular laser</i></p>

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	<p>photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the aflibercept groups could receive laser and patients in the laser group could receive aflibercept. In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score.”); MYL-AFL-BLA1079688 at -1079708–1079709, at section 14.4, tbl. 7 (showing that 33.3% of 2Q8 DME patients (VIVID) and 33.1% of 2Q8 DME patients (VISTA) gained at least 15 letters in BCVA from baseline); MYL-AFL0004715.</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat DME by using the method of claim 10, resulting in a patient gaining at least 15 letters of Best Corrected Visual Acuity (BCVA) score.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 23 to 87 years with a mean of 63 years. Of those, 576 were randomized to aflibercept groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 5 initial monthly injections (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the aflibercept groups could receive laser and patients in the laser group could receive aflibercept. In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score.”); MYL-AFL-BLA1079688 at -1079708–1079709, at section 14.4, tbl. 7 (showing that 33.3% of 2Q8 DME patients (VIVID) and 33.1% of 2Q8 DME patients (VISTA) gained at least 15 letters in BCVA from baseline); MYL-AFL0004715.</p>

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16. The method of claim 15 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.	<p>Administration of aflibercept in accordance with Mylan's proposed labeling practices claim 15 as set forth above.</p> <p>In the DME clinical study results shown in Mylan's proposed labeling, which direct physicians to treat DME using the method of claim 15, the mean change in BCVA was measured by ETDRS letter score from baseline, so the BCVA score corresponded to the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g., MYL-AFL-BLA1079688, at -1079708–1079709, at section 14.4, tbl. 7; MYL-AFL0004715.</i></p> <p>In accordance with Mylan's proposed labeling, physicians will treat DME by using the method of claim 15, where the Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079708–1079709, at section 14.4, tbl. 7; MYL-AFL0004715.</i></p>
17. The method of claim 10 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.	<p>Administration of aflibercept in accordance with Mylan's proposed labeling practices claim 10 as set forth above.</p> <p>Mylan's proposed labeling directs physicians to treat DME using the method of claim 10, excluding patients that have active intraocular inflammation or active ocular or periocular infection.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at Highlights of Prescribing Information (listing as contraindications "Ocular or periocular infection" and "Active intraocular inflammation"); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.1 ("YESAFILI is contraindicated in patients with ocular or periocular infections."); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.2 ("YESAFILI is contraindicated in patients with active intraocular inflammation.").</i></p> <p>In accordance with Mylan's proposed labeling, physicians will treat DME by using the method of claim 10, excluding patients that have active intraocular inflammation or active ocular or periocular infection.</p>

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	<p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (listing as contraindications “Ocular or periocular infection” and “Active intraocular inflammation”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.1 (“YESAFILI is contraindicated in patients with ocular or periocular infections.”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.2 (“YESAFILI is contraindicated in patients with active intraocular inflammation.”).</p>
(18pre) 18. A method for treating diabetic retinopathy in a patient in need thereof,	<p>Mylan’s proposed labeling directs physicians to treat diabetic retinopathy (DR) by administering afibercept.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILITM (afibercept-jbv) is interchangeable* to EYLEA (afibercept.”); MYL-AFL-BLA1079688 at -1079689, at section 1.4 (“YESAFILI is indicated for the treatment of . . . Diabetic Retinopathy (DR”.).</p> <p>In accordance with Mylan’s proposed labeling, physicians will administer afibercept to treat diabetic retinopathy (DR).</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing administration of afibercept to treat, <i>inter alia</i>, diabetic retinopathy (DR)); MYL-AFL-BLA1079688 at -1079689, at section 1.4 (“YESAFILI is indicated for the treatment of . . . Diabetic Retinopathy (DR”.).</p>
(18a) comprising intravitreally administering, to said patient, an effective amount of afibercept which is 2 mg approximately every 4 weeks for the first 5 injections,	<p>Mylan’s proposed labeling directs physicians to treat DR by administering 2 mg of afibercept approximately every 4 weeks for the first 5 injections.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at -1079690, at section 2.5 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections . . . ”).</p>

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	<p>In accordance with Mylan's proposed labeling, physicians will treat DR by administering 2 mg of aflibercept approximately every 4 weeks for the first 5 injections.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at -1079690, at section 2.5 ("The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections . . .").</p>
(18b) followed by 2 mg approximately once every 8 weeks or 2 months.	<p>Following administration of 2 mg of aflibercept approximately every 4 weeks for the first 5 injections, as directed by Mylan's proposed labeling for the treatment of DR, Mylan's proposed labeling directs physicians to administer 2 mg (0.05 mL) of aflibercept via intravitreal injection once every 8 weeks or once every 2 months to treat DR.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at -1079690, at section 2.5 ("The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).").</p> <p>In accordance with Mylan's proposed labeling, following administration of 2 mg of aflibercept every 4 weeks for the first 5 injections, physicians will administer 2 mg (0.05 mL) via intravitreal injection once every 8 weeks or once every 2 months to treat DR.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at -1079690, at section 2.5 ("The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).").</p>
19. The method of claim 18, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.	<p>Administration of aflibercept in accordance with Mylan's proposed labeling practices claim 18 as set forth above.</p> <p>Mylan's proposed labeling instruct physicians that every 4 weeks comprises approximately every 28 days or approximately monthly.</p>

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	<p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at -1079690, at section 2.5 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections . . .”).</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat DR by administering 2 mg of aflibercept every 4 weeks for the first 3 months, where every 4 weeks is approximately every 28 days or approximately monthly.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at -1079690, at section 2.5 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections . . .”).</p>
21. The method of claim 18, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 18 as set forth above.</p> <p>Following administration of 2 mg of aflibercept approximately every 4 weeks for the first 5 injections, as directed by Mylan’s proposed labeling for the treatment of DR, after 20 weeks, Mylan’s proposed labeling directs physicians to administer 2 mg (0.05 mL) of aflibercept once every 4 weeks to treat DR.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at -1079690, at section 2.5 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).”).</p> <p>In accordance with Mylan’s proposed labeling, following administration of 2 mg of aflibercept every 4 weeks for the first 5 injections, after 20 weeks, physicians will administer 2 mg (0.05 mL) via intravitreal injection once every 8 weeks or once every 2 months to treat DR.</p>

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	<p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at -1079690, at section 2.5 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).”).</p>
23. The method of claim 18 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 18 as set forth above.</p> <p>Mylan’s proposed labeling indicates that M710 (YESAFILI) is interchangeable with EYLEA (aflibercept), which, according to Mylan’s proposed labeling, means it is “a biological product that is approved based on data demonstrating that it is highly similar to an FDA-approved reference product (RP) and that there are no clinically meaningful differences between the products; it can be expected to produce the same clinical result as the RP in any given patient; and if administered more than once to a patient, the risk in terms of safety or diminished efficacy from alternating or switching between the use of the RP and IP is not greater than that from the PR without such alternation or switch . Interchangeability of YESAFILI has been demonstrated for the condition(s) of use, strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.” Mylan’s proposed labeling includes the results for clinical studies that assessed the safety and efficacy of aflibercept in studies in patients with DR. Because M710 must be highly similar to EYLEA (aflibercept) and must not have any clinically meaningful differences compared to EYLEA (aflibercept) (the reference product), and because the clinical study results for treating DR by administering aflibercept using the method of claim 18, which are included in Mylan’s proposed labeling, show that patients gained at least 15 letters of Best Corrected Visual Acuity (BCVA) score, Mylan’s proposed labeling directs physicians to administer YESAFILI (M710) to treat DR such that a patient will gain at least 15 letters of Best Corrected Visual Acuity (BCVA) score.</p>

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	<p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILIT™ (aflibercept-jbvf) is interchangeable* to EYLEA (aflibercept.”); MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 23 to 87 years with a mean of 63 years. Of those, 576 were randomized to aflibercept groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 5 initial monthly injections (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the aflibercept groups could receive laser and patients in the laser group could receive aflibercept. In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score.”); MYL-AFL-BLA1079688 at -1079708–1079709, at section 14.4, tbl. 7 (showing that 33.3% of 2Q8 DME patients (VIVID) and 33.1% of 2Q8 DME patients (VISTA) gained at least 15 letters in BCVA from baseline); MYL-AFL-BLA1079688 at -1079710–1079713, at Section 14.5; MYL-AFL0004715; Brown 2021.</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat DR by using the method of claim 18, resulting in a patient gaining at least 15 letters of Best Corrected Visual Acuity (BCVA) score.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 23 to 87 years with a mean of 63 years. Of those, 576 were randomized to aflibercept groups in the two studies (VIVID and VISTA). In each study, patients were</p>

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	randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 5 initial monthly injections (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the aflibercept groups could receive laser and patients in the laser group could receive aflibercept. In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score."); MYL-AFL-BLA1079688 at -1079708–1079709, at section 14.4, tbl. 7 (showing that 33.3% of 2Q8 DME patients (VIVID) and 33.1% of 2Q8 DME patients (VISTA) gained at least 15 letters in BCVA from baseline); MYL-AFL-BLA1079688 at -1079710–1079713, at Section 14.5; MYL-AFL0004715; Brown 2021.
24. The method of claim 23 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.	<p>Administration of aflibercept in accordance with Mylan's proposed labeling practices claim 23 as set forth above.</p> <p>In the DR clinical study results shown in Mylan's proposed labeling, which direct physicians to treat DR using the method of claim 23, the mean change in BCVA was measured by ETDRS letter score from baseline, so the BCVA score corresponded to the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4, tbl. 7; MYL-AFL-BLA1079688 at -1079710–1079713, at Section 14.5; MYL-AFL0004715; Brown 2021.</p> <p>In accordance with Mylan's proposed labeling, physicians will treat DR by using the method of claim 23, where the Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4, tbl. 7; MYL-AFL-BLA1079688 at -1079710–1079713, at Section 14.5; MYL-AFL0004715; Brown 2021.</p>
25. The method of claim 18 wherein exclusion criteria	Administration of aflibercept in accordance with Mylan's proposed labeling practices claim 18 as set forth above.

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for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.	<p>Mylan's proposed labeling directs physicians to treat DR using the method of claim 18, excluding patients that have active intraocular inflammation or active ocular or periocular infection.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (listing as contraindications "Ocular or periocular infection" and "Active intraocular inflammation"); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.1 ("YESAFILI is contraindicated in patients with ocular or periocular infections."); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.2 ("YESAFILI is contraindicated in patients with active intraocular inflammation.").</p> <p>In accordance with Mylan's proposed labeling, physicians will treat DR by using the method of claim 18, excluding patients that have active intraocular inflammation or active ocular or periocular infection.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (listing as contraindications "Ocular or periocular infection" and "Active intraocular inflammation"); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.1 ("YESAFILI is contraindicated in patients with ocular or periocular infections."); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.2 ("YESAFILI is contraindicated in patients with active intraocular inflammation.").</p>
(26pre) 26. A method for treating diabetic retinopathy in a patient with diabetic macular edema, who is in need of such treatment,	<p>Mylan's proposed labeling directs physicians to treat diabetic retinopathy (DR) in a patient with diabetic macular edema (DME) by administering aflibercept.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information ("YESAFILITM (aflibercept-jbvf) is interchangeable* to EYLEA (aflibercept)."); MYL-AFL-BLA1079688 at section 1.4 ("YESAFILI is indicated for the treatment of . . . Diabetic Retinopathy (DR)."); MYL-AFL-BLA1079688 at -1079710–1079713, at section 14.5 ("Efficacy and safety data of aflibercept in diabetic retinopathy (DR) are derived from the VIVID, VISTA, and PANORAMA studies. In the VIVID and VISTA studies, . . . [a]ll enrolled patients</p>

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	<p>had DR and DME at baseline. The majority of patients enrolled in these studies (77%) had moderate-to-severe nonproliferative diabetic retinopathy (NPDR) based on the ETDRS-DRSS. [see <i>Clinical Studies</i> (14.4)]."); MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4 ("Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 23 to 87 years with a mean of 63 years. Of those, 576 were randomized to aflibercept groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 5 initial monthly injections (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed).").</p> <p>In accordance with Mylan's proposed labeling, physicians will administer aflibercept to treat DR in patients with DME.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information ("YESAFILITM (aflibercept-jbvf) is interchangeable* to EYLEA (aflibercept)."); MYL-AFL-BLA1079688 at section 1.4 ("YESAFILI is indicated for the treatment of . . . Diabetic Retinopathy (DR)."); MYL-AFL-BLA1079688 at -1079710–1079713, at section 14.5 ("Efficacy and safety data of aflibercept in diabetic retinopathy (DR) are derived from the VIVID, VISTA, and PANORAMA studies. In the VIVID and VISTA studies, . . . [a]ll enrolled patients had DR and DME at baseline. The majority of patients enrolled in these studies (77%) had moderate-to-severe nonproliferative diabetic retinopathy (NPDR) based on the ETDRS-DRSS. [see <i>Clinical Studies</i> (14.4)]."); MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4 ("Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 23 to 87 years with a mean of 63 years. Of those, 576 were randomized to aflibercept groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 5 initial monthly injections (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed).").</p>

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(26a) comprising intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections	<p>Mylan's proposed labeling directs physicians to treat DR in patients with DME by administering 2 mg of aflibercept approximately every 4 weeks for the first 5 injections.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079690, at section 2.5 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections . . .”).</i></p> <p>In accordance with Mylan's proposed labeling, physicians will treat DR in patients with DME by administering 2 mg of aflibercept approximately every 4 weeks for the first 5 injections.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079690 at section 2.5 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections . . .”).</i></p>
(26b) followed by 2 mg approximately once every 8 weeks or 2 months.	<p>Following administration of 2 mg of aflibercept approximately every 4 weeks for the first 5 injections, as directed by Mylan's proposed labeling for the treatment of DR in patients with DME, Mylan's proposed labeling directs physicians to administer 2 mg (0.05 mL) of aflibercept via intravitreal injection once every 8 weeks or once every 2 months to treat DR in patients with DME.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079690, at section 2.5 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”).</i></p> <p>In accordance with Mylan's proposed labeling, following administration of 2 mg of aflibercept every 4 weeks for the first 5 injections, physicians will administer 2 mg (0.05 mL) via intravitreal injection once every 8 weeks or once every 2 months to treat DR in patients with DME.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079690, at section 2.5 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or</i></p>

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	50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”).
27. The method of claim 26, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 26 as set forth above.</p> <p>Mylan’s proposed labeling instruct physicians that every 4 weeks comprises approximately every 28 days or approximately monthly.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -107690, at section 2.5 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections . . .”).</i></p> <p>In accordance with Mylan’s proposed labeling, physicians will treat DR in patients with DME by administering 2 mg of aflibercept every 4 weeks for the first 5 injections, where every 4 weeks is approximately every 28 days or approximately monthly.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079690, at section 2.5 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections . . .”).</i></p>
28. The method of claim 26, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 26 as set forth above.</p> <p>Following administration of 2 mg of aflibercept approximately every 4 weeks for the first 5 injections, as directed by Mylan’s proposed labeling for the treatment of DR in patients with DME, after 20 weeks, Mylan’s proposed labeling directs physicians to administer 2 mg (0.05 mL) of aflibercept once every 4 weeks to treat DR in patients with DME.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079690, at section 2.5 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections . . .”).</i></p>

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	<p>weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months.”).</p> <p>In accordance with Mylan’s proposed labeling, following administration of 2 mg of aflibercept every 4 weeks for the first 5 injections, after 20 weeks, physicians will administer 2 mg (0.05 mL) via intravitreal injection once every 8 weeks or once every 2 months to treat DR in patients with DME.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079690, at section 2.5 (“The recommended dose for YESAFILI is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months.”).</i></p>
29. The method of claim 26 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 26 as set forth above.</p> <p>Mylan’s proposed labeling indicates that M710 (YESAFILI) is interchangeable with EYLEA (aflibercept), which, according to Mylan’s proposed labeling, means it is “a biological product that is approved based on data demonstrating that it is highly similar to an FDA-approved reference product (RP) and that there are no clinically meaningful differences between the products; it can be expected to produce the same clinical result as the RP in any given patient; and if administered more than once to a patient, the risk in terms of safety or diminished efficacy from alternating or switching between the use of the RP and IP is not greater than that from the PR without such alternation or switch . Interchangeability of YESAFILI has been demonstrated for the condition(s) of use, strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.” Mylan’s proposed labeling includes the results for clinical studies that assessed the safety and efficacy of aflibercept in studies of DR patients with DME. Because M710 must be</p>

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	<p>highly similar to EYLEA (aflibercept) and must not have any clinically meaningful differences compared to EYLEA (aflibercept) (the reference product), and because the clinical study results for treating DR in patients with DME by administering aflibercept using the method of claim 26, which are included in Mylan's proposed labeling, show that patients lost less than 15 letters of Best Corrected Visual Acuity (BCVA) score, Mylan's proposed labeling directs physicians to administer YESAFILI (M710) to treat DR in patients with DME using the method of claim 26 such that a patient will lose less than 15 letters of Best Corrected Visual Acuity (BCVA) score.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILI™ (aflibercept-jbvf) is interchangeable* to EYLEA (aflibercept.”); MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4 (“Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 23 to 87 years with a mean of 63 years. Of those, 576 were randomized to aflibercept groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 5 initial monthly injections (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the aflibercept groups could receive laser and patients in the laser group could receive aflibercept. In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score.”); MYL-AFL-BLA1079688 at -1079708–1079709, at section 14.4, tbl. 7 (showing that the mean change in BCVA as measured by ETDRS letter score from Baseline in DME patients treated with five monthly 2 mg doses of aflibercept followed by 2 mg doses administered once every 8 weeks was 10.7 for the VIVID study and the VISTA study); MYL-AFL-BLA1079688 at -1079710–1079713, at Section 14.5; MYL-AFL0004715; Brown 2021.</i></p> <p>In accordance with Mylan's proposed labeling, physicians will treat DR by using the method of claim 18, resulting in</p>

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	<p>a patient loosing less than 15 letters of Best Corrected Visual Acuity (BCVA) score.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILIT™ (aflibercept-jbvf) is interchangeable* to EYLEA (aflibercept.”); MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4 (“Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 23 to 87 years with a mean of 63 years. Of those, 576 were randomized to aflibercept groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 5 initial monthly injections (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the aflibercept groups could receive laser and patients in the laser group could receive aflibercept. In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score.”); MYL-AFL-BLA1079688 at -1079708–1079709, at section 14.4, tbl. 7 (showing that the mean change in BCVA as measured by ETDRS letter score from Baseline in patients treated with five monthly 2 mg doses of aflibercept followed by 2 mg doses administered once every 8 weeks was 10.7 for the VIVID study and the VISTA study); MYL-AFL-BLA1079688 at -1079710–1079713, at Section 14.5; MYL-AFL0004715; Brown 2021.</i></p>
31. The method of claim 26 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 26 as set forth above.</p> <p>Mylan’s proposed labeling indicates that M710 (YESAFILI) is interchangeable with EYLEA (aflibercept), which, according to Mylan’s proposed labeling, means it is “a biological product that is approved based on data demonstrating that it is highly similar to an FDA-approved reference product (RP) and that there are no clinically meaningful differences between the products; it can be expected to produce the same clinical result as the RP in any given patient; and if administered more than once to a patient, the risk in terms of safety or diminished efficacy</p>

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	<p>from alternating or switching between the use of the RP and IP is not greater than that from the PR without such alternation or switch . Interchangeability of YESAFILI has been demonstrated for the condition(s) of use, strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.” Mylan’s proposed labeling includes the results for clinical studies that assessed the safety and efficacy of aflibercept in studies in DR patients with DME. Because M710 must be highly similar to EYLEA (aflibercept) and must not have any clinically meaningful differences compared to EYLEA (aflibercept) (the reference product), and because the clinical study results for treating DR in patients with DME by administering aflibercept using the method of claim 26, which are included in Mylan’s proposed labeling, show that patients gained at least 15 letters of Best Corrected Visual Acuity (BCVA) score, Mylan’s proposed labeling directs physicians to administer YESAFILI (M710) to treat DR in patients with DME such that a patient will gain at least 15 letters of Best Corrected Visual Acuity (BCVA) score.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILITM (aflibercept-jbv) is interchangeable* to EYLEA (aflibercept).”); MYL-AFL-BLA1079688 at -1079710–1079713, at section 14.5 (“Efficacy and safety data of aflibercept in diabetic retinopathy (DR) are derived from the VIVID, VISTA, and PANORAMA studies. In the VIVID and VISTA studies, . . . [a]ll enrolled patients had DR and DME at baseline. The majority of patients enrolled in these studies (77%) had moderate-to-severe nonproliferative diabetic retinopathy (NPDR) based on the ETDRS-DRSS. [see Clinical Studies (14.4)]..”); MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 23 to 87 years with a mean of 63 years. Of those, 576 were randomized to aflibercept groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 5 initial monthly injections</p>

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	<p>(aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the aflibercept groups could receive laser and patients in the laser group could receive aflibercept. In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score.”); MYL-AFL-BLA1079688 at -1079708–1079709, at section 14.4, tbl. 7 (showing that 33.3% of 2Q8 DME patients (VIVID) and 33.1% of 2Q8 DME patients (VISTA) gained at least 15 letters in BCVA from baseline); MYL-AFL-BLA1079688 at -1079710–1079713, at Section 14.5; MYL-AFL0004715; Brown 2021.</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat DR in patients with DME by using the method of claim 26, resulting in a patient gaining at least 15 letters of Best Corrected Visual Acuity (BCVA) score.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (“YESAFILIT™ (aflibercept-jbvf) is interchangeable* to EYLEA (aflibercept.”); MYL-AFL-BLA1079688 at -1079710–1079713, at section 14.5 (“Efficacy and safety data of aflibercept in diabetic retinopathy (DR) are derived from the VIVID, VISTA, and PANORAMA studies. In the VIVID and VISTA studies, . . . [a]ll enrolled patients had DR and DME at baseline. The majority of patients enrolled in these studies (77%) had moderate-to-severe nonproliferative diabetic retinopathy (NPDR) based on the ETDRS-DRSS. [see Clinical Studies (14.4)].”); MYL-AFL-BLA1079688 at -1079708–1079710, at section 14.4 (“The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 23 to 87 years with a mean of 63 years. Of those, 576 were randomized to aflibercept groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 5 initial monthly injections (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4</p>

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	<p>weeks (aflibercept 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the aflibercept groups could receive laser and patients in the laser group could receive aflibercept. In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score.”); MYL-AFL-BLA1079688 at -1079708–1079709, at section 14.4, tbl. 7 (showing that 33.3% of 2Q8 DME patients (VIVID) and 33.1% of 2Q8 DME patients (VISTA) gained at least 15 letters in BCVA from baseline); MYL-AFL-BLA1079688 at -1079710–1079713, at Section 14.5; MYL-AFL0004715; Brown 2021.</p>
32. The method of claim 31 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 31 as set forth above.</p> <p>In the DR and DME clinical study results shown in Mylan’s proposed labeling, which direct physicians to treat DR in patients with DME using the method of claim 31, the mean change in BCVA was measured by ETDRS letter score from baseline, so the BCVA score corresponded to the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at -1079708–1079709, at section 14.4, tbl. 7; MYL-AFL-BLA1079688 at -1079710–1079713, at Section 14.5; MYL-AFL0004715; Brown 2021.</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat DR in patients with DME by using the method of claim 31, where the Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 -1079708–1079709, at section 14.4, tbl. 7; MYL-AFL-BLA1079688 at -1079710–1079713, at Section 14.5; MYL-AFL0004715; Brown 2021.</p>
33. The method of claim 26 wherein exclusion criteria for the patient include (1) active intraocular	Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 26 as set forth above.

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inflammation; or (2) active ocular or periocular infection.	<p>Mylan's proposed labeling directs physicians to treat DR in patients with DME using the method of claim 26, excluding patients that have active intraocular inflammation or active ocular or periocular infection.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (listing as contraindications "Ocular or periocular infection" and "Active intraocular inflammation"); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.1 ("YESAFILI is contraindicated in patients with ocular or periocular infections."); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.2 ("YESAFILI is contraindicated in patients with active intraocular inflammation.").</p> <p>In accordance with Mylan's proposed labeling, physicians will treat DR in patients with DME by using the method of claim 26, excluding patients that have active intraocular inflammation or active ocular or periocular infection.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (listing as contraindications "Ocular or periocular infection" and "Active intraocular inflammation"); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.1 ("YESAFILI is contraindicated in patients with ocular or periocular infections."); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.2 ("YESAFILI is contraindicated in patients with active intraocular inflammation.").</p>
(34pre) 34. A method for treating an angiogenic eye disorder in a patient in need thereof,	<p>Mylan's proposed labeling directs physicians to treat angiogenic eye disorders by administering aflibercept.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing administration of aflibercept to treat Wet AMD, RVO, DR, and DME); MYL-AFL-BLA1079688 at -1079700, at section 12.1 ("Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PIGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PIGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation</p>

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	<p>of these receptors by VEGF-A can result in neovascularization and vascular permeability. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.”).</p> <p>In accordance with Mylan’s proposed labeling, physicians will administer aflibercept to treat angiogenic eye disorders.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing administration of aflibercept to treat Wet AMD, RVO, DR, and DME); MYL-AFL-BLA1079688 at -1079700, at section 12.1 (“Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.”).</i></p>
(34a) said method comprising administering to the patient an effective sequential dosing regimen of a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;	<p>Aflibercept is a VEGF antagonist.</p> <p><i>See, e.g., MYL-AFL-BLA1079688 at -1079700, at Section 12.1 (“Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.”).</i></p>

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	<p>Mylan contends that M710 (YESAFILI) is a product biosimilar to and/or interchangeable with aflibercept having the same amino acid sequence as aflibercept.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA0013550 (BLA § 3.2.S.1.2.1) (“The amino acid sequence of M710 is identical to that of aflibercept.”); MYL-AFL-BLA1079688 (“YESAFILIT™ (aflibercept-jbfv) is interchangeable* to EYLEA (aflibercept.”).</p> <p>Mylan’s proposed labeling directs physicians to treat wet AMD, DME, and DR by administering a single dose of aflibercept, followed by one or more secondary doses of the aflibercept, followed by one or more tertiary doses of aflibercept.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing that, for the treatment of wet AMD, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months),” and directing that, for the treatment of DME and DR, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months.”).</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat wet AMD, DME, and DR by administering a single dose of aflibercept, followed by one or more secondary doses of the aflibercept, followed by one or more tertiary doses of aflibercept.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing that, for the treatment of wet AMD, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months),” and directing that, for the treatment of DME and DR, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal</p>

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	injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”).
(34b) wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and	<p>Mylan’s proposed labeling directs physicians to treat wet AMD, DME, and DR by administering secondary doses of aflibercept 4 weeks after the immediately preceding dose.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing that, for the treatment of wet AMD, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months),” and directing that, for the treatment of DME and DR, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”).</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat wet AMD, DME, and DR by administering secondary doses of aflibercept 4 weeks after the immediately preceding dose.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing that, for the treatment of wet AMD, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months),” and directing that, for the treatment of DME and DR, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”).</p>
(34c) wherein each tertiary dose is administered 8 weeks after the immediately preceding dose;	<p>Mylan’s proposed labeling directs physicians to treat wet AMD, DME, and DR by administering tertiary doses of aflibercept at least 8 weeks after the immediately preceding dose.</p>

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	<p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing that, for the treatment of wet AMD, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months),” and directing that, for the treatment of DME and DR, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”).</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat wet AMD, DME, and DR by administering tertiary doses of aflibercept at least 8 weeks after the immediately preceding dose.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA1079688 at Highlights of Prescribing Information (directing that, for the treatment of wet AMD, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months),” and directing that, for the treatment of DME and DR, “[t]he recommended dose for YESAFILI is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).”).</p>
(34d) wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor which is VEGFR1 and an Ig domain 3 of a second VEGF receptor which is VEGFR2, and a multimerizing component.	<p>Mylan’s M710, which has an amino acid sequence identical to aflibercept, is a VEGF receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor which is VEGFR1 and an Ig domain 3 of a second VEGF receptor which is VEGFR2, and a multimerizing component.</p> <p><i>See, e.g.</i>, MYL-AFL-BLA0013550 (BLA § 3.2.S.1.2.1) (“The amino acid sequence of M710 is identical to that of aflibercept.”); <i>id.</i> (“M710 is a homodimeric fusion protein in which each chain consists of the 2nd domain of vascular endothelial growth factor receptor (VEGFR)1 and the 3rd</p>

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	domain of VEGFR2 linked to the Fc portion of an immunoglobulin G (IgG)1 heavy chain.”).
35. The method of claim 34 wherein the VEGF antagonist is aflibercept.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 34 as set forth above.</p> <p>Aflibercept is a VEGF antagonist.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at -1079700, at Section 12.1 (“Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PIGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PIGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PIGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.”).</p> <p>Mylan contends that M710 (YESAFILI) is a product biosimilar to and/or interchangeable with aflibercept having the same amino acid sequence as aflibercept.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA0013550 (BLA § 3.2.S.1.2.1) (“The amino acid sequence of M710 is identical to that of aflibercept.”); MYL-AFL-BLA1079688 (“YESAFILITM (aflibercept-jbvf) is interchangeable* to EYLEA (aflibercept.”).</p>
36. The method of claim 35 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.	<p>Administration of aflibercept in accordance with Mylan’s proposed labeling practices claim 35 as set forth above.</p> <p>Mylan’s proposed labeling directs physicians to treat angiogenic eye disorders using the method of claim 35, excluding patients that have active intraocular inflammation or active ocular or periocular infection.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (listing as contraindications “Ocular or periocular infection” and “Active intraocular inflammation”); MYL-AFL-BLA1079688 at -1079694-</p>

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	<p>1079695, at section 4.1 (“YESAFILI is contraindicated in patients with ocular or periocular infections.”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.2 (“YESAFILI is contraindicated in patients with active intraocular inflammation.”).</p> <p>In accordance with Mylan’s proposed labeling, physicians will treat angiogenic eye disorders by using the method of claim 35, excluding patients that have active intraocular inflammation or active ocular or periocular infection.</p> <p><i>See, e.g.,</i> MYL-AFL-BLA1079688 at Highlights of Prescribing Information (listing as contraindications “Ocular or periocular infection” and “Active intraocular inflammation”); MYL-AFL-BLA1079688 at -1079694–1079695, at section 4.1 (“YESAFILI is contraindicated in patients with ocular or periocular infections.”); MYL-AFL-BLA1079688 at section 4.2 (“YESAFILI is contraindicated in patients with active intraocular inflammation.”).</p>